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CONTRIBUTORS TO VOLUME I

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ANDERS, JAMES M., M.D.
BRUCE, DAVID, C.B., F.R.S., D.Sc., M.B., C.M. (Edin.)
CALKINS, GARY N., Ph.D.
CHITTENDEN, RUSSELL H., Ph.D., LL.D.
CRAIG, CHARLES F., M.D.
EDSALL, DAVID L., M.D.
FUTCHER, THOMAS B., M.B.
GORDON, ALFRED, M.D.
HOWARD, L. O., Ph.D.
HUTCHISON, ROBERT, M.D., F.R.C.P. (Lond.)
LAMBERT, ALEXANDER, M.D.
MENDEL, LAFAYETTE B., Ph.D.
NOGUCHI, HIDEYO, Sc.M., M.D.
NOVY, FREDERICK G., M.D.
OSLER, WILLIAM, M.D.
STEPHENS, J. W. W., M.D. (Cantab.)
STILES, CHARLES WARDELL, Ph.D., D.Sc.
STILL, GEORGE F., M.A., M.D. (Cantab.), F.R.C.P. (Lond.)
STRONG, RICHARD P., M.D.
TAYLOR, ALONZO ENGLEBERT, M.D.
WRIGHT, JAMES HOMER, M.D., Hon. S.D. (Harv.)

MODERN MEDICINE

ITS THEORY AND PRACTICE

IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND
FOREIGN AUTHORS

EDITED BY

WILLIAM OSLER, M.D.

REGIUS PROFESSOR OF MEDICINE IN OXFORD UNIVERSITY, ENGLAND; HONORARY PROFESSOR OF MEDICINE IN
THE JOHNS HOPKINS UNIVERSITY, BALTIMORE; FORMERLY PROFESSOR OF CLINICAL MEDICINE IN
THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, AND OF THE INSTITUTES OF MEDICINE
IN MCGILL UNIVERSITY, MONTREAL, CANADA

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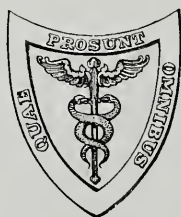
THOMAS MCCRAE, M.D.

ASSOCIATE PROFESSOR OF MEDICINE AND CLINICAL THERAPEUTICS IN THE JOHNS HOPKINS UNIVERSITY,
BALTIMORE; FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, LONDON

VOLUME I

EVOLUTION OF INTERNAL MEDICINE—PREDISPOSITION AND
IMMUNITY—DISEASES CAUSED BY PHYSICAL, CHEMICAL AND
ORGANIC AGENTS—BY VEGETABLE PARASITES—BY
PROTOZOA—BY ANIMAL PARASITES—NUTRITION—
CONSTITUTIONAL DISEASES

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PUBLISHERS' NOTE.

A NEW era has come in medicine, the age of cosmopolitanism. As in finance and trade, the world has become a single country. The cause of this solidarity is to be found in modern improvements in communication which obliterate time, distance and the artificial boundaries of geography, making mankind a single family, and immediately distributing for the benefit of its members the knowledge of every advance, wherever attained. Only one obstacle remains, namely, difference of language, and this, though it will always exist, is practically overcome by the familiarity which the leaders in the profession must now possess with the writings of their compeers in other tongues.

It is more necessary in medicine than in any other sphere of human effort that the world-knowledge should be placed at the command of all. Physicians of the dominant language, English, have just cause for satisfaction in realizing that this is now to be accomplished in their own tongue, and under the leadership of one best fitted, by common consent, to develop this idea in its most complete and fruitful manner. Physician, philosopher, littérateur, he unites in the highest degree all the necessary qualifications for marshalling the leaders in the most beneficent of professions in a great effort for the common good. Nothing has been spared for the full accomplishment of this purpose, and now, from the record of twenty-three centuries, every sincere follower of the masters of medicine has at command a fund of accumulated knowledge greater than any of them could have possessed. The full resources of the modern world have been brought to bear upon this work, and it is now submitted to the profession for judgment as to its conception and execution.

CONTRIBUTORS TO VOLUME I.

- J. GEORGE ADAMI, M.D., F.R.S.,
Professor of Pathology in the McGill University, Montreal, Canada.
- JAMES M. ANDERS, M.D.,
Professor of the Theory and Practice of Medicine and Clinical Medicine in the
Medico-Chirurgical College; Consulting Physician to the Jewish Hospital
Association of Philadelphia; Consulting Physician to the Widener Home for
Crippled Children, Philadelphia.
- DAVID BRUCE, C.B., F.R.S., D.Sc., M.B., C.M. (EDIN.),
Colonel, British Army,
- GARY N. CALKINS, Ph.D.,
Professor of Protozoölogy in the Columbia University, New York City.
- RUSSELL H. CHITTENDEN, Ph.D., LL.D.,
Professor of Physiological Chemistry in the Sheffield Scientific School of Yale
University, New Haven, Conn.
- CHARLES F. CRAIG, M.D.,
First Lieutenant and Assistant Surgeon in the U. S. Army.
- DAVID L. EDSALL, M.D.,
Assistant Professor of Medicine in the University of Pennsylvania, Medical
Department, Philadelphia.
- THOMAS B. FUTCHER, M.B.,
Associate Professor of Medicine in the Johns Hopkins University; Associate
in Medicine in the Johns Hopkins Hospital, Baltimore, Md.
- ALFRED GORDON, M.D.,
Associate in Mental and Nervous Diseases in the Jefferson Medical College,
Philadelphia; Examiner of the Insane at the Philadelphia General Hospital;
Neurologist to the Mt. Sinai and Douglas Memorial Hospitals, Philadelphia.
- L. O. HOWARD, Ph.D.,
Chief of the Bureau of Entomology of the U. S. Department of Agriculture,
Washington, D. C.
- ROBERT HUTCHISON, M.D., F.R.C.P. (LOND.),
Assistant Physician to the London Hospital and to the Hospital for Sick Chil-
dren, Great Ormond Street, London, England.
- ALEXANDER LAMBERT, M.D.,
Professor of Clinical Medicine in the Cornell University Medical College;
Attending Physician in the Bellevue Hospital, New York City.
- LAFAYETTE B. MENDEL, Ph.D.,
Professor of Physiological Chemistry in the Sheffield Scientific School, Yale
University, New Haven, Conn.

HIIDEYO NOGUCHI, Sc.M., M.D.,

Assistant of the Rockefeller Institute for Medical Research, New York City.

FREDERICK G. NOVY, M.D.,

Professor of Bacteriology in the University of Michigan, Ann Arbor, Mich.

WILLIAM OSLER, M.D.,

Regius Professor of Medicine in Oxford University, England.

J. W. W. STEPHENS, M.D. (CANTAB.),

Walter Myers Lecturer on Tropical Medicine in the University of Liverpool, Liverpool, England.

CHARLES WARDELL STILES, Ph.D., D.Sc.,

Chief of the Division of Zoölogy in the Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, Washington, D. C.

GEORGE FREDERIC STILL, M.A., M.D. (CANTAB), F.R.C.P. (LOND.),

Professor of Diseases of Children in King's College, London; Physician for Diseases of Children in King's College Hospital; Assistant Physician to the Hospital for Sick Children, Great Ormond Street, London, England.

RICHARD P. STRONG, M.D.,

Director of the Biological Laboratory; Professor of Tropical Medicine in the Manila Government Medical School, Manila, P. I.

ALONZO ENGLEBERT TAYLOR, M.D.,

Professor of Pathology in the University of California, Medical Department, San Francisco, Cal.

JAMES HOMER WRIGHT, M.D., Hon. S.D. (HARV.),

Assistant Professor of Pathology in the Medical School of Harvard University; Director of the Pathological Laboratory of the Massachusetts General Hospital, Boston, Mass.

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INTRODUCTION.

THE EVOLUTION OF INTERNAL MEDICINE.

By WILLIAM OSLER, M.D.

I.

SCARCELY twenty years have passed since the completion of Pepper's *System of Medicine*. The distinguished ability of its Editor and the important group of contributors with whom he was associated combined to produce a treatise which profoundly influenced medicine in America. Twenty years are a very brief space of time, but science has been progressing with extraordinary rapidity, sufficient to make even that important work out-of-date, though not in all particulars. As in Reynolds' *System*, in Virchow's *Handbuch*, and in von Ziemssen's *Encyclopedia*, so in that *System* there are articles which still retain their freshness, and must for many years be valuable for reference. Meanwhile in England Allbutt's *System*, now in a second edition, has proved a worthy successor to Reynolds. In Germany, where such publications are planned on a vast scale in comparison with the American and English works, the great *Handbuch* of Nothnagel, in twenty-four volumes, has just been completed; and a selection from the volumes is appearing in English dress. The days of the Encyclopedias in France appear to have passed, at any rate years have gone since the issue of the last volume of Dechambre; but the *Traité* of Charcot and Bouchard has passed through two editions, and there have been issued several works of a similar character, though on a less extensive scale. American publishers have shown no little enterprise in the same direction. The *System of Medicine*, by Loomis and Thompson (1897-1898); *The Twentieth Century Practice of Medicine* (1895-1900); Buck's *Reference Handbook*, second edition (1900-1904), and the American edition of selected volumes from Nothnagel's *System*, already referred to, have been of the greatest service to the profession.

The need for new works of this type is strongly emphasized by a comparison of the present volume with the first volume of Pepper's *System*. It seems scarcely credible that in so many directions in so short a time the entire outlook on the science of medicine can have been so revolutionized. To give three instances in illustration: our views on heredity have been profoundly modified by the studies of Weismann, Mendel, and others, and we are fortunate in *Modern Medicine* to have the subject presented by Professor Adami in so clear and attractive a manner that it will be most helpful to all students. In no direction has there been such progress as in our knowledge of the chemical processes of the body. At the same

time the necessarily imperfect state of organic chemistry has given an undue prominence to certain half-truths, and no department of medicine has lent itself more easily to pseudo-science. The elaborate sections by Professor Taylor and by Professor Chittenden illustrate how surely we are reaching a position of accurate and sound knowledge. More particularly is this the case with the complicated processes of normal metabolism, and we are in consequence better able to understand and study intelligently the perversions met with in disease. No articles in this volume are deserving of more careful study by all who wish to appreciate the new standpoint in physiological and pathological chemistry. In 1885 we had not realized clearly our position with regard to the infectious diseases. The extension of our knowledge of the causative agents of the acute infections has been followed by a study of the laws of immunity, which has not only revolutionized general pathology, but has also opened out new lines of treatment. Vaccines, antitoxins, curative sera of various kinds have been discovered, and with this rapid progress it is not astonishing that at times we have gone too fast and too far, and that there have been the disappointments and failures invariably associated with human endeavor, but these only serve to bring into sharper contrast the solid results which the labor of two decades has secured. No single advance is more striking than that relating to our knowledge of the protozoa as causes of disease. The brilliant researches of Theobald Smith on Texas fever were the first to make the profession appreciate the part which this class of organisms played in the acute infections, and gave, moreover, the demonstration of a scientific method and insight of a most remarkable character.

II.

Like other departments of philosophy, medicine began with an age of wonder. The accidents of disease and the features of death aroused surprise and stimulated interest, and a beginning was made when man first asked in astonishment, Why should these things be? Surrounded everywhere by mysteries, he projected his own personality into the world about him, and peopled heaven and earth with Powers, responsible alike for the good and for the evil, who were to be propitiated by sacrifices or placated by prayers. Satisfying the inborn longing of the human mind for an explanation, these celestial creatures of his handiwork presided over every action of his life. For countless ages man regarded disease as a manifestation of these powers; the evil eye and demoniacal possession, the murrain on the cattle, and the sickness that destroyeth in the noon-day had alike a supernatural origin. Crude and bizarre among the primitive nations, these ideas of disease received among the Greeks and Romans a practical development worthy of these great peoples. There have been systems of so-called divine healing in all the great civilizations, but, for beauty of conception and for grandeur of detail in the execution, all are as nothing in comparison with the cult of the Son of Apollo, of Æsculapius, the God of healing. To him were raised superb structures which were filled with the most sublime products of Greek art, and which were at once temples and sanatoria. Among the most important

were those of Cos, Cnidos, Epidaurus, Croton, Cyrene and Rhodes. The elaborate ritual of the cure is well described in the *Plutus* of Aristophanes. Real cures were often effected and the inscriptions tell of the touching and simple faith which, then as now, forms so important a factor in the healing of many diseases. In other cases change of air and scene, the baths, and massage effected a cure. Hypnotism (?), diet, gymnastic exercises, and games formed part of the treatment. In dreams which came in the "temple sleep" the god indicated the special treatment to be carried out. These temples were really sacred sanatoria situate in beautiful localities and greatly resorted to by people of all classes. At first they appear to have had close associations with the secular medicine of the day and to have represented depositories of empirical knowledge, but later they become hot-beds of jugglery and deception.

Scientific medicine, the product of a union of religion with philosophy, had its origin in a remarkable conjunction of gifts and conditions among the Greeks in the fifth and sixth centuries. "There was the teeming wealth of constructive imagination united with the sleepless, critical spirit which shrank from no test of authority; there was the most powerful impulse to generalization coupled with the sharpest faculty for descrying and distinguishing the finest shades of phenomenal peculiarity; there was the religion of Hellas, which afforded complete satisfaction to the requirements of sentiment, and yet left the intelligence free to perform its destructive work; there were the political conditions of a number of rival centres of intellect, of a friction of forces excluding the possibility of stagnation, and, finally, of an order of state and society strict enough to curb the excesses of 'children crying for the moon,' and elastic enough not to hamper the soaring flight of superior minds." We have already made acquaintance with two of the sources from which the spirit of criticism derived its nourishment, the metaphysical and dialectical discussions practised by the Eleatic philosophers and the semi-historical method which was applied to the myths by Hecateus and Herodotus. A third source is to be traced to the schools of the physicians. These aimed at eliminating the arbitrary element from the view and knowledge of nature, the beginnings of which were bound up with it in a greater or less degree, though practically without exception and by the force of an inner necessity. A knowledge of medicine was destined to correct that defect, and we shall mark the growth of its most precious fruits in the increased power of observation and the counterpoise it offered to hasty generalizations, as well as in the confidence which learned to reject untenable fictions, whether produced by luxuriant imagination or by *a priori* speculations, on the similar ground of self-reliant sense perception."¹

Greek medicine did not originate with Hippocrates, who in reality represents to us the embodiment of a period in which he only forms the most striking figure. As he remarks in the book *On Ancient Medicine*, "but all these requisites belong of old to medicine, and an origin and way have been found out by which many and elegant discoveries have been made during a length of time, and others will yet be found out, if a person possessed of the proper ability, and knowing these discoveries

¹ Gomperz, *Greek Thinkers*, vol. i.

which have been made, should proceed from them to prosecute his investigations."¹ At the two most famous of the Æsculapian temples, Cnidos and Cos, rational medicine began to develop about the sixth century B.C. "It was not the priests who were the pioneers of progress, but the temple doctors, the so-called Asclepiads, who in historic times had a very slight connection with the cult, possibly none whatever, and were free to practise their calling, at their own discretion, outside the sacred precincts or even in foreign countries. In any case in the century immediately preceding the time of Hippocrates, the Asclepiads of Cnidos or Cos were only a sharply defined group of Greek doctors, distinguished from the rest by a rigid organization which found expression in definite rules and formalities. These had for their object to incorporate in the guild of Asklepios those only who, closely united by their common veneration of the god of healing, and by similar scientific opinions, made it their goal to excel in the practice of medicine. They bound themselves by oath to maintain the dignity of the art, to preserve a high morality in the practice of their calling, to show gratitude toward their teachers, fraternal feeling toward the offspring of those teachers, and to guard against profanation of the secrets of their profession."²

The view of disease in the Hippocratic writings shows how strong was the influence of the philosophers, particularly of Empedocles and Pythagoras. As in the *Macrocosm* there were four elements, fire, air, earth, and water, so in man, the *Microcosm*, there were four elements, blood, mucus, yellow bile, and black bile, of which the blood represented the heat, the mucus the cold, the yellow bile the dryness, the black bile the moisture. Health consisted in a harmony or due admixture of these humors, disease in a dyscrasia or imperfect admixture. This humoral pathology of the Hippocratic school dominated the profession for more than two thousand years. From Pythagoras may be traced directly the doctrine of critical days, which still lingers in the profession and of which one hears among the laity. Hippocrates introduced into medicine the art of observation, the critical judgment of observed facts, and a rational induction from them, freed from speculation and theory. This has been the objective, practical method followed since his day by all the great masters of medicine, and it has been the instrument by which we have obtained our descriptive knowledge of disease. Briefly stated, from the Greeks we obtained in the first place the conception of medicine as an art based on careful observation, and as a science an integral part of the science of man and of nature; and, secondly, those high moral ideals which have always inspired the profession, so well expressed in the Hippocratic oath, which has been called one of the most memorable of human documents.

After the death of Hippocrates Greek medicine continued to flourish under the Macedonian *régime*, and at Alexandria, with the fostering care of the Ptolemies, reached a very high plane. Anatomy and physiology, in particular, were studied with the greatest care and many important discoveries were made, particularly by Herophilus and Erasistratus.

¹ This is brought out very clearly in Mollet's *La Médecine chez les Grecs avant Hippocrate*, 1906.

² Neuberger, *Geschichte der Medizin*, vol. i.

Had we full knowledge of the writings of these two great physicians we should probably find that they had made many valuable observations in clinical medicine and pathology. For example, Erasistratus described ascites with great care, and knew of its associations with hardening of the liver and disease of the spleen.

In the intellectual capture of Rome by the Greeks, medicine played a not inconsiderable part, and Greek physicians rose to positions of dignity and importance which have rarely since been equalled in any country or at any period by the leaders of our profession. One of these, Asclepiades, the founder of the school of Methodists, opposed the prevailing humoral pathology and placed the changes met with in diseases largely in the solids of the body. The Methodists made no special contribution to diagnosis, but Asclepiades seems to have been a shrewd and careful physician, placing greater stress upon exercise, baths, massage, and diet than upon the treatment of disease by medicines. The centuries immediately preceding and following the birth of Christ saw medicine flourish remarkably throughout the Roman world. In addition to the Methodists there were the Dogmatists, the Eclectics, the Pneumatists, from none of whom did medicine receive any very fertile contributions. Clinically one of the most interesting figures of this period is Aretæus, whose works have a strong Hippocratic flavor and whose clinical pictures of disease have rarely been equalled. The student who wishes to get a picture of Greco-Roman medicine of this period should read, on the one hand, Celsus, who gives a remarkable summary of the medical and surgical knowledge of the day, and, on the other, Pliny, whose descriptions abound with the fads and fancies of popular medicine.

The great Greek practitioner of the period, and in some ways the greatest figure in the history of medicine, is Galen, who was born in Pergamos about the year A.D. 130. He lived only for part of his life in Rome, where he was the physician to successive emperors and occupied a position of commanding dignity. In every department of medicine this remarkable man was a reformer and an innovator. In opposition to the prevailing views of the Empirics and the Methodists, he placed the whole foundation of the art in anatomy and physiology. He restored the Hippocratic methods and the humoral pathology of the master. Galen's researches in anatomy were of the most extensive character, and in this subject, as well as upon the nature and treatment of disease, his views were accepted as gospel until the Renaissance. The four humors were somewhat modified by him under the influence of the Pneumatics, who introduced the doctrine of the spirits—animal, natural, and vital—which so long held sway. The special interest to us here is that to him may be traced the second great instrument which has influenced the advance of clinical medicine, namely, experiment. He was the first great experimental clinician. We owe to him elaborate studies upon the action of the heart, and he narrowly missed discovering the general circulation of the blood. He made careful observations on the physiology of respiration, and recognized the difference between diaphragmatic and intercostal breathing. By experiments on the nervous system he demonstrated the differences between the motor and the sensory nerves, and even distinguished the motor and sensory roots leaving the spinal cord. In these and other studies he far eclipsed his predecessors, and as an

experimenter he had no successor of the same calibre until Harvey. In treatment he was a follower of Hippocrates, trusting to nature, and both diet and gymnastics played an important role in his system. Greek medicine had now reached its climax, and with Galen the first great chapter in the history of scientific medicine closes. It is one of the most remarkable and in a way an inexplicable feature in history that, having made a beginning of such brilliancy, the scientific study of disease should have made little or no progress for the next fourteen or fifteen centuries. Into the causes of this sterility this is not the place to inquire. During the long period three great names ruled all minds, Ptolemy, Aristotle, and Galen, and men were content to accept the geographic system of the one, the natural history and philosophy of the other, while the infallibility of the great Pergamite became the first article of belief among all practitioners of medicine.

Through the middle ages the continuity of Greek medicine was maintained, first, by the writers of the Byzantine school, whose works are of value chiefly as compilations, of which those of Oribasius and Paul of Ægina are the most important; and secondly, by the Arabians, who came in contact with Greek medicine in the East and in Egypt. For them Aristotle and Galen were the great masters, but departing from the plain methods of observation and induction, Arabian writers rejoiced in dogmatism and subtle dialectics. They introduced a new pharmacy with many new drugs from the East, and with them came many new chemical processes. Sadly mixed as it was with alchemy, in their crude science we find the germs of modern chemistry. Some of the Arabians became great clinicians and made notable and accurate contributions to clinical medicine. To Rhazes we owe the first good account of smallpox. They also recognized measles. Avicenna became the greatest name in Arabian medicine, and throughout the latter part of the middle ages his authority rivalled that of Galen. There was a third narrow stream through which Greek medicine was preserved, namely, the old Universities, and particularly the school of Salernum in Southern Italy. In the early middle ages, from the tenth to the twelfth centuries, it maintained the Greek tradition and was recognized as the leading school of medicine in Europe. Though its derivation is unknown, the school possessed a continuity in thought with the old Greek writers. Later the school of Salernum became tinged with Arabian medicine, but through it the writings of Galen and Hippocrates, mixed with the accretions from Arabian sources, filtered into modern Europe.

Practically throughout the middle ages there was no such thing as an accurate study of clinical medicine. In what is known as the scholastic period, the three centuries before the Renaissance, authority and dogma ruled supreme, and philosophy and medicine alike were a confused jumble of Greek and Arabian authorities. The Renaissance influenced clinical medicine in three ways: First, it restored once and for all the methods of Hippocrates and of Galen. The careful study of descriptive anatomy by Vesalius and his successors restored to men the lost art of clear, independent vision. Secondly, in the revolt against dogmatism and authority a new chemistry arose, at first, in the hands of Paracelsus and others, crude and unscientific, yet it laid the foundation for all our subsequent studies, and through van Helmont and the seventeenth

century chemists has led to the present most fruitful results. Thirdly, we may trace as a direct effect of the Renaissance the revival of experiment in medicine which had been introduced by Galen. The work on metabolism by Sanctorius, and the demonstration by Harvey of the circulation of the blood gave an immense impetus to the scientific investigation of the functions of the body and of the causes of disease. It cannot be said that Harvey's work had any very special influence on clinical medicine except in conjunction with the mechanical philosophy of Descartes and the foundation of the so-called iatro-mechanical school. How little actual progress had been made in clinical medicine is illustrated by what a leading practitioner, Willis, in the middle of the seventeenth century thought of such a disease as inflammation of the lungs. The essential cause was believed to be that the blood boiled feverishly, and "sticking within the more narrow passages of the lungs engendered there an obstruction causing inflammation." Neither in the description of the symptoms nor in the discussion of the prognosis is there any radical advance upon the position of Hippocrates and of Galen. A case, the particulars of which he gives, shows the heroic character of the treatment: "I drew blood twice or thrice day after day." "Frequent clysters were administered; moreover, apozems, juleps, also spirits of ammoniac and powder of fish shells were administered by turns." When phlebotomy was no longer safe very large blisters were applied to the arms and thighs. One is surprised to learn that the patient recovered, but he suffered greatly from the blisters which did "run hugely and afterwards for almost a month daily discharged great plenty of a most sharp ichor."

III.

Not truly scientific and uninfluenced by his friends, Boyle and Locke, (who appreciated fully the importance of the scientific movement of the day), Sydenham restored in a measure the practical methods of the Hippocratic school, careful observation, guided by common sense. If to that remarkable conception of diseases as objects of study and classification, as in the subjects of botany and natural history, Sydenham had added the methods of Harvey, experiment and postmortem observation, the real revolution in clinical medicine might not have had to wait until the beginning of the nineteenth century. A prince among practical physicians, the limitations imposed upon himself restricted his view, and Sydenham never got to the "seats and causes of disease" as did his great successor, Morgagni; but as a portrayer of their objective features he has had few equals, and in this he even bettered the instruction of his master, Hippocrates. In his study of fevers Sydenham displayed a remarkable independence, not more in the graphic pictures which he has left us than in his insistence upon the importance of a knowledge of their natural history as a basis of rational treatment. That he was led away by too great belief in an epidemic constitution was only to be expected in so close a follower of Hippocrates. No one before him had so clearly grasped the conception that the manifestations of a fever represented the efforts of nature to get rid of the injurious agents causing the disease. Many of his descriptions of chronic diseases have never been surpassed, and his

account of chorea, of hysteria, and of gout have become classical in the literature. But it was in treatment that he showed a still more revolutionary spirit. He had a supreme faith in nature as the true healer, to whom the physician played a secondary part, assisting her when she was feeble, restraining her when excessive and violent. That many diseases got well if left to themselves was a novel doctrine in the seventeenth century. But it was in his new method of treating fever, and particularly smallpox, by cooling measures, plenty of drink and fresh air, that he departed most strongly from the practice of his day and achieved signal success. One of the most interesting figures in the history of clinical medicine, Sydenham has impressed his method on his countrymen, who have always cared less for the theoretical conceptions than for the practical, common-sense aspects in the consideration of disease. Several of Sydenham's contemporaries in England were keen clinical physicians who have left on record valuable contributions to medicine. Glisson in particular may be mentioned as a man in whom were combined the anatomical and clinical features so characteristic of the teachers of this period. His treatise, *de Rachidide*, 1650, is the first extensive monograph on a single disease published in England (Cains' *Sweating Sickness*, published a century earlier, had not the same ambitious scope). Not only are the clinical aspects of the disease given in great detail, but the morbid anatomy and the etiology also are fully discussed. Morton, too, was an admirable systematic writer and his works *Pyretologia* (1692) and *Phthisiologia* (1689) show accurate study, and the subjects are presented in a more orderly and logical way than in the writings of Sydenham.

Brilliant and even revolutionary as was the work of this small group of English physicians, it did not immediately influence the progress of clinical medicine until the advent of the Dutch Hippocrates, Boerhaave, upon whom fell the mantle of Sydenham. But meanwhile there had arisen on the Continent the iatro-physical school, based upon the mechanical conceptions of the Cartesian philosophy and supported by the experiments of Sanctorius, of Harvey, of Borrelli and others. Silvius, of Leyden, and Pitcairn, Mead and Friend were the chief exponents of this system, in which everything was explained in terms of mathematical reasoning; and while it did good service in combating the dominant doctrine of the humors, the extravagance of its professors hastened the downfall of a school which, after all, rested on a strong basis of truth.

As with nearly everything of value in the practical aspects of modern life, agriculture, horticulture, banking, colonization, etc., so in clinical medicine the Dutch were our masters. The great Italian teachers of the sixteenth and seventeenth centuries were also practitioners, and there must have been some instruction in the art as well as in the science of medicine, but it was everywhere desultory and unsystematic until the Dutch physicians organized regular clinical instruction as part of the University teaching. Professor Pell tells me that the hospital clinic at Utrecht preceded that at Leyden, but it was at this latter place, under the influence of Boerhaave, that it became most effective. The history of this University illustrates the importance of men in forming an educational centre; students flocked to it from all parts of Europe to sit at the feet of such teachers as Silvius, Grotius, the younger Scaliger, Bidloo, and Pitcairn. After teaching botany and chemistry, Boerhaave succeeded

to the chair of physic in 1714. With an unusually wide general training, a profound knowledge of the chemistry of the day, and an accurate acquaintance with all aspects of the history of the profession, he had a strongly objective attitude of mind toward disease, following closely the methods of Hippocrates and Sydenham. He adopted no special system, but studied disease as one of the phenomena of nature. His clinical lectures, held bi-weekly, became exceedingly popular and were made attractive not less by the accuracy and care with which the cases were studied than by the freedom from fanciful doctrines and the frank honesty of the man. He was much greater than his published work would indicate, and, as is the case with many teachers of the first rank, his greatest contributions were his pupils. No teacher of modern times has had such a following. Among his favorite pupils may be mentioned Haller, the physiologist, and van Swieten, the founder of the Vienna school.

Edinburgh had had very close affiliations with Leyden, and one of Boerhaave's predecessors was Archibald Pitcairn, who subsequently returned to his native city and had an important influence in building up the university, the medical school of which was not organized until 1726. The Leyden methods of instruction were introduced by pupils of Boerhaave, of whom John Rutherford was the most distinguished. He began to teach at the Royal Infirmary in 1747. I have a manuscript of his clinical lectures delivered in the winter session of 1748-49, from which we may get a good idea of his plan of teaching. He says: "The method I propose to pursue is, to examine every patient before you, lest any circumstances should be overlooked. I shall undertake this by a plan which will be the most useful I can think of. I shall give you the history of his disease in general; secondly, inquire into the cause of it, and, thirdly, give you my opinion how the disease is likely to terminate and lay down the indication of cure, or when any extraordinary symptoms arise you shall have notice of it that you may see the reason of altering my prescriptions."

Those were happy days for the medical student, as a few paragraphs later he says: "I do not mean by this that you should all take degrees, for I am far from thinking that a diploma furnishes a man with medical knowledge. His improvement in this art depends on his own study and industry." Three, four, and even five patients were shown on the same day, and great care was taken to keep the students informed of the progress of patients who had been seen by them. Weeks afterward a memorandum is given, perhaps, of the postmortem. The history, the symptoms, and the prognosis are very well considered, but one misses the physical examination and an accurate consideration of the pathology and morbid anatomy. Groups of cases were considered together, as illustrated by Lecture 23, in which a series of cases of scurvy, that had been "in the house," were considered together.

Directly inspired from Leyden, the Edinburgh school soon outstripped all its compeers. In the main thoroughly practical and objective, as witnessed, for example, in the work of Whytt, it illustrated also the speculative nature of the Scottish character in two systems of medicine which had great vogue. Cullen, who was Whytt's successor in the chair of institutes, became the most prominent teacher of medicine in his day in

the English-speaking world. He was a most inspiring lecturer and a thoroughly good clinical teacher. While, perhaps, it is scarcely correct to say that he introduced a system, yet he was the first to attach special importance to the nervous system as influencing disease. A more definite system, comparable with the older ones which prevailed on the Continent in the seventeenth and eighteenth centuries, was the Brunonian, introduced by John Brown, a pupil of Cullen. The essence of this consisted in an insistence upon debility as the fundamental factor in disease, and the necessity of always maintaining a supporting line of treatment. Few systems of medicine have ever stirred such bitter controversy, and in Charles Creighton's account of Brown¹ we read that as late as 1802 the University of Göttingen was so convulsed by controversies on the merits of the Brunonian system that contending factions of students in enormous numbers, not unaided by the professors, met in combat in the streets on two consecutive days and had to be dispersed by a troop of Hanoverian horse.

In England and the colonies the influence of the Edinburgh school became supreme. London had no properly organized medical teaching. In the hospitals the surgeons gave good instruction and there was an admirable system of pupils and dressers. But to medicine proper little or no attention had been paid. One of the physicians of the hospital lectured on medicine, materia medica, and chemistry, chiefly to men who were to become apothecaries or general practitioners. To take the M.D. degree, men had to go to Edinburgh or abroad, or they took the Oxford or Cambridge M.D., after keeping a certain number of terms. Throughout the eighteenth century the methods and practice of Boerhaave had great influence in London. Many of the Fellows of the College of Physicians had been his pupils. His works were translated and frequently reprinted, but, without university organization and without systematic instruction, the clinical teaching was carried on in a very desultory manner. Toward the end of the century several men trained in Edinburgh methods became distinguished teachers and workers in the London hospitals, of whom William Saunders may be taken as an example. A pupil of Cullen, he became in 1770 physician to Guy's Hospital and at once began to lecture upon medicine and to give clinical instruction. He was a hard worker and a keen clinical observer, as his papers on lead colic, on the diseases of the liver, and on delirium tremens amply testify. Gilbert Blane and Matthew Baillie were both Glasgow men. The latter, a graduate of Oxford, was the best clinical physician of his day in London, but no doubt he got most of his pathological and clinical training from his uncles, William and John Hunter. Fothergill and Lettsom, Halford, Holland, Bright, Paris, Humphry Davy, Caleb Parry, and Marshall Hall were Edinburgh men.

To Edinburgh all the abler young men from the English colonies went for their medical education. Bard, Morgan, Shippen, Rush, Wistar, Hossack and others brought back to America the traditions and methods of its schools; and it was not until the third decade of the nineteenth century that the tide of students turned toward France. Early in that decade it was a group of young Edinburgh men, Holmes, Robertson,

¹ *Dictionary of National Biography.*

Stevenson, and Caldwell, who began medical instruction in Montreal, from which originated the Medical Faculty of McGill College.

Boerhaave and his pupils extended the range of observation and in a measure restored to medicine that robust common sense which had been the distinguishing feature of both Hippocrates and Sydenham. At the end of the eighteenth century men were floundering in a sea of speculation and there was no definiteness in diagnosis nor any safe basis for treatment. The next great step came from an extension of the Hippocratic method to the dead-house, the study of morbid anatomy in association with clinical observation.

IV.

Many of the sixteenth and seventeenth century physicians had keen appreciation of the value of postmortem examinations. Harvey has a most interesting paragraph on the subject,¹ and his works testify to the zeal with which he sought for the more hidden causes of disease; but with no one in the seventeenth century did morbid anatomy become a life study, and no one had realized its true position in the science of medicine until Morgagni (1683-1771) published the *De Sedibus et Causis Morborum per Anatomen Indagatis* (1761). Others before this date had made interesting collections of cases: Ridley in England, and Bonetus of Geneva, who published the *Sepulcretum Anatomicum* in 1679. Valuable as is this great work, it had not the profound influence of the *De Sedibus*, as it was a collection of cases from the literature, and lacked that freshness and interest which Morgagni was able to give to his reports. In them for the first time we find a careful clinical study of the symptoms of disease and an equally careful examination of the organs after death. It was the novelty of the mode of presentation quite as much as the vivid picture of disease that made Morgagni's work mark an epoch in the history of clinical medicine. Even today it is a storehouse of valuable facts, and several of the sections, more particularly that on the heart and bloodvessels, are so rich in original descriptions that no man's education in morbid anatomy can be said to be complete without an acquaintance with its pages. The example of the great Italian was soon followed in other countries, particularly in England and in France. John Hunter, with his insatiable hunger for knowledge of all sorts, was equally great as a morbid- and as a comparative anatomist. The Hunterian specimens in the great Museum at Lincoln's Inn Fields bear witness to the accuracy of his descriptions, to the insistence, when possible, upon clinical details, and to the keen appreciation which he had of the importance of the study of morbid anatomy in the education of medical men. His brother William, also an enthusiastic student of morbid anatomy, formed an important collection, and the specimens and notes in his museum, now at Glasgow, show that he too was alive to the value

¹ "The examination of a single body of one who has died of tabes or some other disease of long standing, or poisonous nature, is of more service to medicine than the dissection of the bodies of ten men who have been hanged." Letter to Riolan.

of the new method of combining clinical with anatomical work. Matthew Baillie, their nephew, gave to the world the fruits of their researches, combined with his own, in the *Morbid Anatomy* published in 1793 and followed in 1799 by his well-known *Atlas*. Texts and plates, alike admirable, formed the most important contribution to practical medicine made in England during the eighteenth century, if we exclude Jenner's vaccinations. The *Series of Engravings* was the first of its kind to be published, and the accuracy of the drawings and the careful descriptions made it for years a standard work, and indeed the plates may still be used in illustrating lectures. But the new science reached its fullest development in France, and helped to promote the revolution in clinical medicine which was effected in that country during the first three decades of the nineteenth century. To the school of Bichat, who was essentially a morbid anatomist, we owe the fruitful studies which gave us our modern outlook on the processes of disease. Corvisart and Bayle, Broussais, Laennec, Louis, Chomel, and Andral revived *Das Anatomischen Denken* (Virchow) of Morgagni.

With the old Hippocratic method, however, which had been used for centuries, and which Morgagni had simply transferred from the bedside to the dead-house, it would have been impossible to get beyond the great Italian. Hitherto the sense of sight had dominated in the examination of the patient, supplemented to some extent by the sense of touch. Now the hand and ear were to take an equal share, and the eye was to have its powers enormously extended by the use of the microscope. From the *Inventum Novum* of Auenbrugger (1761) we may date the introduction of modern clinical methods into medicine. His discovery illustrates the fate of a truth announced prematurely. The time was not ripe, and the art of percussion had to await the keen mind of Corvisart before its importance was recognized. The greatest stimulus ever given to internal medicine was the discovery of auscultation by Laennec, whose work *L'Auscultation Médiate* (1819) not merely introduced a new method, but was also a treatise on diseases of the heart and lungs, combining the results of clinical study and anatomical investigation. With this book began an entirely new era in medicine. Rich in the descriptions of diseases hitherto unrecognized and unrecognizable, this immortal work not only placed a new and powerful method in the hands of physicians, but also gave an enormous stimulus to the study of internal diseases. The researches of Louis correlated the symptoms and physical signs with the anatomical appearances in pulmonary tuberculosis and in typhoid fever. Chomel, Andral, Bretonneau, Rayer, Piorry, Cruveilhier and others caught the new spirit and made Paris the centre of medical instruction for the whole world. This revolution in internal medicine was effected simply by an extension of the Hippocratic method from the bedside to the dead-house and by the correlation of the signs and symptoms of a disease with its anatomical appearances. It was by this method that Richard Bright opened up an entirely new chapter in his studies on the relation of disease of the kidneys to dropsy and to albuminous urine. It had already been shown by Blackwell and by Wells, the celebrated Charleston (S. C.) physician, that the urine contained albumin in many cases of dropsy, but it was not until Bright began a careful investigation of the bodies of patients who had presented these symptoms, that he discovered the

association of various forms of disease of the kidney with anasarca and albuminous urine. In no direction was the harvest of this combined study more abundant than in the complicated and confused subject of fever. The work of Louis and of his pupils, W. W. Gerhard and others, revealed the distinction between typhus and typhoid fever, and so cleared up one of the most obscure problems in pathology.

Throughout the nineteenth century this clinico-pathological investigation of disease has widened enormously our diagnostic powers, and the physician today who wishes to obtain a sound knowledge of the natural history of disease must adopt Morgagni's method of "anatomical thinking." Skoda in Vienna, Schoenlein in Berlin, Graves and Stokes in Dublin, Marshall Hall, C. J. B. Williams, and many others introduced the new and exact methods of the French and created a new clinical medicine. A very strong impetus was given by the researches of Virchow on cellular pathology, which removed the seat of disease from the tissues, as taught by Bichat, to the individual elements, the cells. The introduction of the use of the microscope in clinical work widened greatly our powers of diagnosis, and we obtained thereby a very much clearer conception of the actual processes of disease. In another way, too, medicine was greatly helped by the rise of experimental pathology, which had been introduced by John Hunter, was carried along by Magendie and others, and reached its culmination in the epoch-making researches of Claude Bernard. Not only were valuable studies made on the action of drugs, but also our knowledge of cardiac pathology was revolutionized by the work of Traube, Cohnheim, and others. In no direction did the experimental method effect such a revolution as in our knowledge of the functions of the brain. Clinical neurology, which had received a great impetus by the studies of Todd, Romberg, Lockhart, Clarke, Duchenne and Weir Mitchell, was completely revolutionized by the experimental work of Hitzig, Fritsch and Ferrier. Under Charcot the school of French neurologists gave great accuracy to the diagnosis of obscure affections of the brain and spinal cord, and the combined results of the new anatomical, physiological, and experimental work have rendered clear and definite what was formerly the most obscure and complicated section of internal medicine.

The latter part of the nineteenth century saw a complete revolution in our conception of the etiology of infectious diseases. The idea of a *contagium vivum*, of a living agent which multiplied in the body and caused the symptoms of disease, had long been entertained, and the analogies between the fermentation of fluids and disease had been frequently suggested. The brilliant researches of Pasteur placed the bacterial origin of certain diseases on a firm scientific basis. Grasping the idea that the putrefactive and suppurative processes in wounds were due to bacteria, Lister revolutionized surgery, and has made possible operations which have widened enormously the work of surgeons, with a result that today our art is more medico-chirurgical than it has ever been before. But the full importance of the new studies was not realized until Robert Koch discovered in rapid succession the causes of several of the most destructive of epidemic diseases. Then with Laveran's description of the malarial parasite came the recognition of the importance of protozoa as causes of disease. All this work has modified clinical medicine in several important directions. The detection of specific parasites has been

a great help to diagnosis, as, for example, in tuberculosis. The knowledge of the precise etiology has enabled us to take intelligent precautions for the prevention of the disease, and the measures for sanitary control of the acute infections have been strengthened a hundredfold by the studies of the past quarter of a century. In another direction the new science has had a most fruitful application. With the introduction of vaccination against smallpox, Jenner laid the foundation for the modern work, still only in its beginnings, which deals with vaccines, antitoxins, and curative sera. When one considers the comparatively short space of time which has elapsed since Koch's discovery of the tubercle bacillus, we may be grateful that so much has been accomplished, and in spite of many disappointments the situation is one full of hope for the future.

However produced, the ultimate processes of disease represent chemical changes in the fluids and tissues of the body, and in this direction, too, the advances of the past half-century have had a profound influence on clinical medicine. Our knowledge of normal metabolism has progressed with startling rapidity and warrants the belief that before long we shall have a safe platform from which to investigate "to a finish" such serious perversions as are present in gout, diabetes, etc. Already the studies upon internal secretions have not only given us a clear conception of the functions of certain organs, but have also enabled us to treat successfully such otherwise incurable maladies as myxœdema. From the new science of physical chemistry much may be expected, and one of the most encouraging signs is the increasing attention paid by the younger physicians to problems which demand the most accurate chemical technique. In the immediate future it is along chemical lines that we may look for the greatest advance, and of this there is no more satisfactory indication than the simultaneous appearance quite recently in England and the United States of journals devoted to biochemistry.

V.

A work of the scope of the present one has a very different value to different persons. It is designed primarily for the practitioner who wishes to keep himself informed of the existing state of our knowledge in clinical medicine. Elaborate discussions upon doubtful problems have been avoided, and, as far as possible, a clear statement is given without unnecessary references to the literature. Authors have been selected who are acknowledged authorities, and while it is not always easy for a writer who is saturated, so to speak, with his subject to keep within limits, and to remember the practical character of the men for whom he is writing, I hope we have been able to keep an even balance between the condensation of the text-book and the elaborate treatment of the monograph. The first consideration in a work of this kind is that it shall be helpful. To fulfil this requirement we have had sometimes to introduce matter which may seem foreign to a system of medicine. A section on Protozoa, for example, such as that given by Professor Calkins, is indispensable for the appreciation of the importance of this class of parasites, and in a brief article written for the purpose the practitioner will get information of a character better suited to his needs

than from a manual of zoölogy. So, too, for the study and prevention of malaria and of yellow fever a knowledge of the structure, varieties, and life history of the mosquito is necessary, but the most recent information of this sort is not easily to be had from ordinarily procurable books.

There are several ways in which a work of this kind may be most helpful to a man in general practice. It may put him on the right course and give him his bearings when he has been blown about without compass by every wind of doctrine. For instance, studied carefully, the masterly presentation of the subject of Auto-intoxication by Dr. Taylor, in the present volume, will give him the "light and leading" necessary for an intelligent appreciation of one of the most complex and confused departments of medicine. While much remains to be done, we have enough positive knowledge to enable us to approach the clinical side of the question in an intelligent manner, unburdened from much of the nonsense of the auto-intoxication propaganda of the past twenty years. Accurate clinical investigation must accompany chemical research, and, while the two cannot often be combined by a man in active practice, there is no reason why he should not appreciate the problem with sufficient clearness to enable him to furnish unbiased observations of the greatest value and to give to his patients the benefit of the most advanced scientific knowledge. Since upon diet more than upon any other single factor depends the health of the community, it behooves every physician to give to this subject his closest attention. In fully one-half of the patients he is called upon to treat, indigestion plays a most important role, and this may be traced to improper food, improper methods of preparation, or to faulty habits of eating. The real difficulty is less with the profession than in getting the public to carry out certain plain and well-recognized rules. The Yale studies bring into prominence the importance of new views which will appeal strongly to physicians who have long held that we all take too much food and particularly too much meat. From the important section on Metabolism by Professors Chittenden and Mendel the practitioner will get the scientific data upon which he may base rational plans of dietetic treatment in many diseases, and much information of the greatest use in his incessant propaganda against the gastronomic follies of the public. In these and in other sections the authors will be found to have simplified the abstruse and complicated knowledge of the chemical laboratories, and to have presented it in a form readily assimilable by the men who have to use it. Such, I believe, is the chief function of a system of medicine.

VI.

It cannot be too often or too forcibly brought home to us that the hope of the profession is with the men who do its daily work in general practice. Our labors are in vain—all the manifold contributions of science, the incessant researches into the complex problems of life, normal and perverted, the profound and far-reaching conclusions of the thinkers and originators—all these are *Nehushtan*, sounding brass and tinkling cymbals, unless they result in making men better able to fight the battle against disease, better equipped for their ministry of healing. Gradually, often

insensibly, the practical advances of the laboratory and of the hospital reach the men with whom, after all, rests the final testing of all our efforts. The work in practical sanitation, the last word in the prevention of disease, the carrying out new methods of treatment, the exchange of the old accoutrements for the new weapons and the new methods of warfare, these rest with the rank and file of the profession who make effective and translate into practice the new knowledge.

The medical journals, the medical societies, the post-graduate schools all help in this good work, and both the profession and the public now appreciate how important it is that physicians should keep well abreast of the times. The difficulty lies often with the individual men who fall into routine and slovenly habits of practice, and who never get more than a superficial smattering of the science and of the art of medicine. Even the most industrious and ambitious, absorbed in a limited field, find it hard to get new life into the old material, and, confronted on all sides by difficult problems which press for solution, they turn for aid to the men who have made these problems their special study, and it is in such works as the present that these teachers and workers embody or codify, so to speak, the current knowledge of the day.

After all, the important question for each young man to ask himself as he begins practice is: How can I carry on my education so as to get the best possible returns out of life and do the best that is in my power for my fellow-creatures? There are several cardinal defects which stand in the way of the evolution of the sound clinical practitioner: *Lack of preliminary practical training.* The medical curriculum is not yet so arranged as to give our young men enough clinical work in their senior years. So full and complicated has the course become that it is very hard for the teachers to adjust it to the new conditions. We ask too much, and expect too much, of the student; but if we could have him properly prepared at the schools and colleges, if everywhere the preliminary sciences were taught *outside* the medical school, there would be no difficulty in giving a man in four years a good start in his profession, and this is all that the best of teachers in the best of medical schools can do for him. In our well-organized physiological, anatomical, histological, embryological, chemical (physiological), pharmacological, and pathological laboratories the teaching has become more and more thorough and practical, but when we come to the "bread and butter" subjects we are not always prepared to give teaching of the same character. The hospitals and dispensaries are numerous enough, and there is no lack of patients; but there is not that constant, close, personal contact of student with patient in which alone the art of medicine can be learned. There is not that control of hospitals by the universities necessary to ensure proper facilities for students, nor are the arrangements of the hospitals always such as to meet the demands of modern clinical work. There is still too much theoretical teaching for senior students, and in a majority of the schools the number of teachers in medicine, surgery, obstetrics and the specialties is wholly inadequate. In only a few hospitals is the out-patient department arranged for clinical teaching, and the clinical laboratory is not everywhere recognized as a *sine qua non*. If we could turn our third and fourth year students into the hospitals and make them part and parcel of its machinery (just as much as the nurses who have

usurped, I fear, some of their duties, and have advantages that they do not possess) we could give them at least a good introduction to their life-work; and a man could enter upon practice with a rational outlook on disease, and be prepared to continue his education with the help, not at the expense, of the public. But all this is changing rapidly, and year by year the men who leave our schools are better educated and in every way better fitted to practise medicine intelligently. *Lack of critical judgment* is another serious obstacle in the way of the young man. It is hard to get life's spectacles adjusted, so hard to get clear vision, where so much is obscure. The faculty of "right judgment in all things" is granted to few men, but the physician to be of any value must at least aspire to that round-about common sense which was so distinguishing a feature in Sydenham. It may be cultivated, but with caution, as it is one of the virtues more readily acquired when not too consciously sought. Slow of growth, and the fruit of a seasoned experience, good clinical judgment only comes with careful study, and is best seen in men who appreciate the value of thoroughness in their work. The mental attitude controls the course of a man's evolution as a clinical physician. While nothing can be more fatal than a cold Pyrrhonism in which everything is doubted, in the midst of so much credulity, lay and professional, it is well for the young man to take as a motto the saying of that wise old pre-Hippocratic poet-physician, Epicharmus, of Syracuse: "Be sober and distrustful; these are the sinews of the understanding." Credulity is of the very essence of human nature and we physicians are not exempt from the common lot. Our work is an incessant collection of evidence, weighing of evidence, and judging upon the evidence, and we have to learn early to make large allowances for our own frailty, and still larger for the weaknesses, often involuntary, of our patients. The history of medicine is full of instances of self-deception on the part of the best of men, and it is well that the young man should at the outset be humble, as he is not likely to escape altogether. Science has done much in revolutionizing mankind, but man remains the same credulous creature as he has been in all ages. Tar-water, Perkin's tractors, laying on of hands, Christian Science, Lourdes, and the other miracle-working shrines illustrate the deep, intense credulity from which science has not yet freed mankind and is not likely to do so. It is an aspect of human nature which we must accept and sometimes utilize, remembering the remark of Galen: "He cures the greatest number in whom most men have most faith."

It is for the practitioner to make the new facts of science efficient and useful, to translate science into practice. Often a very prolonged affair from inherent difficulties connected with the complicated mechanism of man's body, this is sometimes a source of discouragement, and we hear complaints of the slowness of progress in medicine, and of the inability of physicians at once to turn to practical account some striking discovery. The history of science teaches us that it takes many years from the announcement of the fact to its full application. From Faraday's work on electromagnetic induction to the making of dynamos for commercial purposes was a longer period than from Claude Bernard's discovery of internal secretion to the successful treatment of a case of myxœdema with thyroid extract. In making a new application of science the stages are well defined. First there is the discovery of the phenom-

enon capable of utilization. Then comes an inventor who recognizes the possibility of its practical application. He may require the help of a skilled engineer who correlates the commercial and manufacturing conditions to be dealt with; and finally there is the capitalist who furnishes the means to make the invention of practical utility. In the science of medicine, to make efficient in every-day practice the new discoveries regarding the functions of the body and the phenomena of disease is a very difficult matter. There is much knowledge which cannot always be made helpful. It may add to the clearness of the clinical picture and enable us perhaps to recognize the nature and state of a disease without benefiting in the slightest the poor victim of it. A knowledge of the structure and of the functions of the motor paths may be of no use whatever in a case of complete destruction by a clot in the internal capsule; but in the very next case, one of syphilis of the brain, or in one of tumor of the cord, in the full utilization of this same knowledge may rest the issues of life and death. Just as in the mechanical sciences, it takes a combination of human activities in several stages of effort to reap the benefit of any discovery, so it is in medicine. The anatomist, the physiologist, the pathologist, the clinician, and the surgeon—in as many stages as from Faraday's discovery of electromagnetic induction to the manufacture of a dynamo—all had to combine before a brain tumor could be removed successfully. Between Claude Bernard's discovery of internal secretion and the cure of a case of myxœdema every department of medicine was taxed. To be exploited prematurely in practice is the common fate of all new scientific facts. Not content to wait for full knowledge, men hastily draw conclusions from imperfect data. Consider the dross with which the pure gold of Claude Bernard's discovery has been mixed in an organotherapy often as irrational as that practised in the middle ages.

VII.

Intertwined as the subject is with the complicated sciences of physiology, organic chemistry, and physics, to make solid contributions to clinical medicine we must systematize the work much more than has hitherto been possible. The trustees and managers of hospitals should appreciate more fully than they do at present the scientific needs of these institutions. To do justice to the patients, to carry out modern lines of treatment, indeed, to diagnosticate skilfully, require now the assistance of trained laboratory workers who should form part of the staff. It is impossible for any man, no matter how industrious, to keep abreast at all points with the chemical and bacteriological technique. Two important changes are necessary before hospitals are in a position to do the best possible work in clinical medicine:

First, in many institutions the number of attending physicians should be reduced. In small hospitals of a total capacity of one hundred and fifty beds the medical wards should be placed in charge of one man. In the larger city hospitals separate medical services should be arranged with from sixty to one hundred beds in each. The profession should learn to recognize the worker in internal medicine as a man who has to devote so much time to his studies that it is impossible for him to take general

practice, and in a way he is a specialist, in the broad sense of the term, like the surgeon. The development of clinical medicine is retarded by the present system of appointing general practitioners, often the busiest and most successful men, in charge of the wards. Nowadays only under exceptional circumstances does a man of energy and perseverance evolve from these surroundings into a thoroughly trained clinical investigator. In saying this I do not forget that from these conditions arose the very men who have contributed most to medicine in America, men of the stamp of W. W. Gerhard, Austin Flint, Da Costa and Pepper. But the times are changing, and I know that I express the feelings of hospital physicians themselves when I state that a reorganization is urgently demanded along the lines here indicated. Not only in the larger cities, but in towns of from fifty to one hundred thousand inhabitants the *well-equipped medical clinic is the most urgent need of the profession*. Secondly, the internal organization of the hospitals must be changed to meet the new demands. A larger number of house physicians is required, who should be graded so that raw, inexperienced graduates should not be put at once in full charge of patients. A clinical laboratory with chemical and bacteriological assistants should be provided for each service, or, in the smaller hospitals, one would suffice for all departments. This need, now generally recognized for hospitals connected with medical schools, is of equal importance in the smaller hospitals. An example of what organization can do in this direction is afforded by the remarkable clinic which has been built up in Rochester, Minnesota, by the Mayo brothers, who have made that little town a world-known resort for both physicians and surgeons, and whose success has been due as much to their careful attention to the laboratory side of their work as to the technique for which they have become so famous.

Lastly, my earnest hope is that this series of volumes may be of service in that education which each one of us has to work out for himself in practice. Set on the right path in the schools it should not be difficult for a man to keep in touch with the advances of science, and to give his patients the benefit of all those accessories which are so important in the recognition and successful treatment of disease. Just as the clinical laboratory is a necessity to the hospital physician engaged in the solution of the most advanced problems in medicine, so the private laboratory is indispensable in the every-day work of the busy practitioner. Urine analysis, blood counts, sputum examinations, chemical analysis of stomach contents, all these should be done at home: at first, by the physician himself, while not too busy; later by an assistant. This may seem to be asking a great deal in the heavy routine of the day, but it is not asking too much, and it will be done more and more when we send out our students familiar by long practice with the use of the microscope and other instruments of precision. It makes the practice of medicine of absorbing interest when one feels he is approaching the study of a case equipped with modern methods, and it is the neglect of these accessories that makes so many men fall into slipshod habits of diagnosis, and still more careless methods of treatment. Asked the single most powerful weapon today in the hands of the profession against quackery of all sorts, I would answer: the little laboratory room attached to the office of the general practitioner. Nor is it asking

the impossible. I know many busy men who utilize to the full all these resources of our art. I would like to call the attention of my colleagues to the papers on this question by my friend, M. H. Fussell,¹ of Philadelphia. Nor is it impossible in general practice to become an active and valued contributor to the literature of the profession. It should not be forgotten that Robert Koch was a district physician when he made his memorable researches upon anthrax. One of the most distinguished scholars of his day was Robert Adams, a village surgeon.

The young physician should not be disturbed by the thought that it requires special abilities to rise superior to one's environment. It is the average man with a set and steady determination to equip himself at all points who is more likely to succeed than any other. The way is open to all. For those whose training in the medical school has been defective the post-graduate school is available, and a month or two every few years spent at a good hospital and in laboratory work add to a man's mental capital and make him of greater value to the public and to his colleagues.

It is astonishing how much there is in the daily round if men would but keep the open mind and look upon life as a progressive education. The times have changed, and we have travelled far from the days when the father of medicine jotted down his notes upon fever cases in Abdera and elsewhere. We know more and enjoy larger opportunities, and with them have greater responsibilities, but could Hippocrates return he would find no change in those essential duties in which he is still our great exemplar. They are four: so to study our cases as to acquire facility in the art of diagnosis, which must everywhere precede the rational treatment of disease; so to grow in critical judgment that we may learn to appreciate the relative value of the symptoms and physical signs, and give to the patient and to his friends a forecast or prognosis; so to conduct the treatment that the patient may be restored to health at the earliest possible period, or, failing that, be given the greatest possible measure of relief, whether by drugs, the action of which he should carefully study, so as to have a strong and abiding faith in those which have been tried and not found wanting, by diet, by exercise, or by all the physical means available, and often by the exercise of his own strong personality; and, lastly, so to arrange sanitary and hygienic measures that, wherever possible, disease may be prevented. Could Hippocrates meet again a class of students at some modern Cos, and discuss the changes which twenty-five centuries had wrought, he would dwell upon this latter development of the science and of the art as the crowning benefit which the profession has bestowed upon the race, and he would repeat again those noble words which have found in this triumph their practical realization: To serve the art of medicine as it should be served, one must love his fellow-men.

¹ *The University Medical Magazine*, 1891, 1896, 1898, 1900. *The Journal of the American Medical Association*, 1901, 1902. *The Philadelphia Medical Journal*, 1901, 1902.

PART I.

HEREDITY AND PREDISPOSITION.

CHAPTER I.

INHERITANCE AND DISEASE.

By J. G. ADAMI, M. A., M. D., F. R. S.

It is difficult to realize that the essential nature of procreation has been known to us for scarce a generation. That the conjugation of the two parents is essential, was obvious *ab ovo*; that there resulted from that union an individual possessing characteristics referable to both parents, was equally clear; nay, more: it was well known that characters not pronounced in the parents but traceable to an earlier generation on either side could, not infrequently, be made out. But why this should be, remained a profound mystery. True it is that Leeuwenhoeck, in 1677, demonstrated the existence of spermatic filaments in the seminal fluid of various animals, yet for close on two centuries the part played by these spermatozoa was a matter of debate. Only in 1852 was it clearly established that the spermatozoön penetrates the envelope of the ovum; only in the "seventies" was it determined through the researches of Van Beneden (1875) and later by those of Strassburger, O. Hertwig, Fol, and Boveri, that the changes following the entrance of the spermatozoön into the ovum, centre round the fusion of the nuclear material of the one with that of the other, and that from the moment of this fusion dates the beginning of the life history of a new individual.

Stated in the simplest terms, the new individual is the result of the union of a single cell from the male parent with a single cell from the female. These two cells are in their turn the derivatives of cells which, from a very early period of embryonic life, can be seen to have been segregated for reproductive purposes, and apparently for nothing else.¹ The individual

¹ Recent studies by Bouin and Ancel demonstrate that the internal secretion of the testicles, and the influence which the presence of this again exerts upon the general metabolism, is connected not with the germinal epithelium (the cells of the tubules), but with certain characteristic interstitial cells lying between the tubules. For a very clear *résumé* of the extent to which the germ-cells are thus segregated from an early period in the different genera of animals, see Bigelow's article on "Heredity," *Buck's Reference Hand-book of the Medical Sciences*, 4, '02, 650.

ova already exist at birth, and lie latent, or at most very slowly increase in size until close upon the time when they are to be discharged. The spermatozoa similarly are derived from cells of, apparently, a simple undifferentiated type, and are developed from these shortly before they are discharged. In other words, neither ovum nor spermatozoön is the result of a piecing together of contributions from the various tissues and organs of the body; neither is a microcosm—a microscopic representation of the adult organism. They are not pangenetic; both are derived from the germinal tissue, which is evidently set apart from the first, so as not to be subjected to the performance of functions other than those of reproduction. The only functions we can recognize as performed by them, prior to their liberation, are assimilation and growth, and, in the case more particularly of the male germ-cells, concomitant multiplication.

When we come to study the details of the process of fusion we find that while the cell-substance of the fertilized ovum is contributed by the female cell and the centrosome¹ by the male, the one constituent contributed with a remarkable quantitative equality by both cells, is the nuclear material, or chromatin.² So striking, in fact, are the preparatory changes in connection with the nucleus of each cell, so elaborate the *contredanse* which precedes the fusion of the nuclear materials of the two cells, that no other conclusion is possible than that here in this fusion of nuclear material is the central act of sexual reproduction; and once we accept—as we are forced to accept—that there may be equally and interchangeably inheritance of features peculiar to either parental stock,³ we are

¹ E. B. Wilson and Naohide Yatsu have brought forward positive proof that the centrosome is not of nuclear origin, but can be reformed in the cytoplasm of cells deprived of their nuclei (Proc. Soc. Exp. Biology and Medicine; *American Medicine*, 1905, p. 493).

² To this statement a reservation must be noted as the result of the recent studies of Henking, Montgomery, McClung of Kansas, and E. B. Wilson. Among hemipterous insects the sperm mother cells give rise to spermatocytes of two orders, so that in certain species one-half of the future spermatozoa receive an "accessory" chromosome; in other species what is a peculiarly large chromosome in the one set of cells is represented by a minute chromosome in the other. The ova of these insects in their development exhibit no such difference. As McClung first noted (*Biological Bulletin* 3, 1902, 43) the only distinction which separates the resultant fertilized cells into two approximately equal groups is *sex*, and we are logically forced to the conclusion that the peculiar chromosome has some bearing upon this differentiation. The distinction has thus far been established for the hemiptera alone. In other insects (Aphides) two types of ova have been noted giving rise to male and female respectively. Thus it is not yet possible to make any general statement regarding differentiation of chromosomes and the determination of sex. Even in these cases it is but one or an uneven pair out of the series of chromosomes that is implicated; sets of chromosomes of varying size and shape are to be recognized in the nuclei that undergo fusion, and these pair with remarkable accuracy (*Vide* Arnold and Moore, *Proceedings of the Royal Society, Series B.*, 77, 1906, 563).

³ The most striking example of this equality of the male and female elements is contained in the observations of von Gärtner (confirmed by Mendel and others) upon the hybridization of peas, in which by the cross-fertilization of two different species ("A" and "B") it was found that identical hybrids were produced whether the pollen of A was employed to fertilize the egg-cells of B, or the pollen of B to fertilize the egg-cells of A. It is true we do not get this happening among mammals. Your mule, the offspring of a jackass and a mare, is a different animal from the hinny or jennet, the offspring of a stallion and a jenny-ass; but here it must be recalled that the inter-uterine development, within the donkey and the mare respectively, must materially modify the progeny in these two cases.

forced to conclude that what is inherited is contained in, and carried by, the nuclear chromatin. From this it follows surely that the only conditions which are capable of being inherited, are conditions which have told upon and modified the nuclear material of the germ-cells of either parent prior to or at the moment of fusion. *It is at that moment of fusion that the new individual begins its existence. Any influence acting upon and modifying it after this moment is something acquired by what is already a separate entity; it is not inherited.*

Starting from this basis, and for the nonce accepting Virchow's dictum that every departure from the normal in the individual is to be regarded as a pathological condition, we are led to classify all pathological conditions (including variations, modifications, and actual conditions of disease) into:

- (1) *Inherited conditions*—
 - a. Derived from the male parental stock.
 - b. Derived from the female parental stock.
 - c. Due to fusion and interaction of the two nuclear materials.
- (2) *Acquired conditions*—
 - a. Of ante-natal acquirement.
 - b. Of parturient acquirement.
 - c. Of post-natal acquirement.

CONDITIONS MISTAKENLY REGARDED AS INHERITED.

And now to clear the ground. It is obvious from the above that many conditions commonly described as inherited are of ante-natal acquirement. Yet other conditions presuppose influences at work on the nuclear matter of the germ-cells of either parent which by no mental effort we can conceive as bringing about the declared results. It will be well to dismiss all these before passing on to consider the conditions truly inherited.

Maternal and Paternal Impressions.—The belief in these as causes of local bodily disturbances has not wholly died out, and in the United States, as McMurrich indicates,¹ judging from the relative amount of literature on the subject, it dies a hard death. Even could we accept the view that through the influence of the maternal nervous system—for it could under the circumstances only be by this—conditions affecting one area of the maternal organism could reproduce themselves upon the corresponding area in the offspring, the overwhelming majority of the cases cited are clearly not examples of inheritance; for in that majority, studying the histories given, the maternal impression has occurred after conception, and most often after the second month of pregnancy; *i.e.*, the period when the offspring passes from the embryonic to the foetal stage, when already the different organs have received their outline and are recognizable as such.

Of maternal and paternal impressions stated to have been in action prior to fertilization, the recorded instances are few and far between. The *locus classicus* is Jacob's stratagem to increase his flock of ring-straked,

¹ McMurrich: *The Physician and Surgeon*, (Ann Arbor,) January, 1905. For full studies of this subject see also Tartuffi, *Storia della Teratologia*, Bologna, 1881-1894; and Ballantyne, *Trans. Edin. Obstetr. Soc.*, 21, 1896.

spotted and speckled sheep and goats at the expense of Laban, his father-in-law. The most recent instance that has come to our notice is that of a well-known Aberdeen breeder of shorthorns, who is convinced that his failure during a recent season to obtain calves having the proper marking—all those cast showing a patch of white on the flank—was due to the fact that instead of the bull serving the cow in the obscurity of the byre, for a time service was conducted in the yard where the family washing was hung out to dry. The cases upon record, in short, are so rare, and the causes adduced so bizarre, that even if we accept the histories given, it is unnecessary to discuss possibilities. The cases are not more frequent than would occur under the law of chance—a law too often neglected in seeking for an explanation of rare conditions. But if this does not satisfy, it may be asked by what conceivable means can a visual impression affecting either parent at the time of conception, influence either spermatozoön or ovum, when both have become free cells, liberated from organic connection with the parental organisms? There is this difference between the domestic animals and man, that in the latter, conjugation occurs irrespective of periods of the dehiscence of the ova, and these, therefore, may still, in the female, have loose organic connection with the parental organism. Even then it may be asked, how can preconceptional nerve stimuli in the mother so alter the molecular arrangement of the nuclear material of an individual ovum as to induce a minute specific difference in the progeny?

The Non-inheritance of Mutilations.—It is obvious from the premises laid down that gross mutilations of the limbs or trunk of either parent cannot reproduce themselves in the offspring; and as a matter of fact, every experiment made with due regard to scientific accuracy demonstrates that this is the case. One may, following Weismann, cut off the tails of twenty successive generations of long-tailed mice—cut them off immediately after birth—cut them off not in one but in both parents—and the twenty-first generation will be born with tails as long and with as many vertebrae as those of the first.

These conclusions have been violently contested, and that because the Lamarckian theory of evolution is based upon the transmission of characters acquired or further developed by the parent—so that could it be found that gross changes in the paternal and maternal organism were inherited, it would have to be conceded that changes of all orders are similarly capable of inheritance. Now it is worthy of note that not a single *series* of experiments has been devised by the Lamarckians which has demonstrated this inheritance of mutilations. Individual cases they have adduced in which the offspring, through one or more generations, have shown defects which more or less definitely imitated the outcome of an injury received by one or other parent-member of an earlier generation. But in the absence of absolute experimental proof, which, if mutilations of any order are transmissible, ought to be forthcoming without difficulty, these isolated instances must again be regarded as coming under the law of chance.

Circumcision, we know, has been practised from time immemorial by certain oriental nations, and practised shortly after birth among the Jews, according to their history, for at least six score generations; but the males are still born with fully developed prepuces. It has been urged recently as evidence of the inheritance of mutilations that a greater proportion of

Jews are born with shortened foreskin and exposed glans than is found among nations which have not practised this rite. This, however, is no argument. The only valid proof would be afforded if it could be demonstrated that the number of naturally circumcised Jews had been undergoing a steady increase during the last thousand years, while no such increase has shown itself in an allied race of the uncircumcised. It may indeed be suggested as eminently probable that circumcision arose, not primarily as a religious rite, but as a hygienic measure of considerable importance in tropical and subtropical regions, and, if so, it must have been based upon not an occasional observation, but upon the common experience that those "naturally circumcised" escaped the troubles to which those having the fully developed foreskin were subjected. In other words, cases of shortened foreskin must have been fairly frequent in those races before circumcision came into vogue.

There is one series of experiments that is constantly adduced in this connection—the celebrated observations of Brown-Sequard upon guinea-pigs rendered epileptic by sundry injuries to the nervous system, the offspring of which were found, some of them, to manifest epileptic and other nervous phenomena. These observations have been confirmed by one group of observers (Westphal and Obersteiner), and have been contradicted by others (Sommer and Binswanger). There is no need to enter fully into these cases, because on the face of them they do not enter into the present category. Only by a confusion of ideas are they included as evidence of the transmission of mutilations or injuries. Epilepsy is not a specific anatomical injury; it is the expression of a functional irritation of the higher nervous centres, set up often by injury at a distance—in Brown-Sequard's cases by injury to the sciatic nerve, etc.; and none of those who adduce these cases demonstrate the transmission to the offspring of the local disturbances which in the parent had induced the epilepsy. At most, these cases come under the heading of the inheritance of acquired functional modifications, which is quite another matter and will be discussed subsequently.

There are, however, two instances recorded by Brown-Sequard which have a bearing in this controversy and cannot be passed over without notice. He noted that one of the progeny of a guinea-pig, which exhibited atrophy of a hind limb following upon section of the sciatic nerve, was born with an ill-developed hind limb, and that similarly one of the progeny of another guinea-pig whose eye had been destroyed, suffered also from an imperfectly developed eye. I do not doubt Brown-Sequard's veracity—that would be absurd; nor will I pretend to explain these cases. I will only say that they are at variance with human experience and that I cannot accept them as examples of inherited mutilations. Whenever the father or the mother has lost a limb, it is a surely ascertained fact that the children are born with the full complement of limbs; and similarly the accidental destruction of an eye in man is known to be without effect on the children. Neither Brown-Sequard nor any one else has been able to repeat these observations at will, or to show how these results can be reproduced. Again I must class them as chance occurrences.

Until, therefore, some supporter of the Lamarckian theory can arise and bring forward an experimental mutilation upon one or other animal which is transmitted and reproduces itself *not as an exception* but in a

reasonable proportion of the offspring of the mutilated animals, we are forced to adhere to the view that *gross mutilations are not transmitted*—and what is more, must urge that we cannot conceive any such transmission.

The Non-inheritance of Specific Infectious Diseases.—Like considerations indicate that it is impossible for there to be inheritance proper of infectious diseases. *There is no such thing as inherited small-pox, inherited tuberculosis, or hereditary syphilis.* For consider what such inheritance necessitates. All infectious disease, we admit now-a-days, is brought about by the growth of pathogenic microörganisms within the system. It is by the nuclear material of the spermatozoön and of the ovum that the parental properties are conveyed to the offspring; it is the molecular composition of that nuclear material that controls the organism of the developing individual. Granted that the inert ovum before conception could take up pathogenic bacteria—or, what is still more opposed to general principles, that the bacteria actually made their way into the ovum; granted, again, that the spermatozoön—a mass of nuclear material and little more—could similarly come to contain a pathogenic microbe: in not one of these cases would the microbes be a part or portion of the heritable matter; they would but be associated. At most the disease would be transmitted from parent to offspring by means of the germ-cells; it would not be strictly inherited.

It may be urged that this is a refinement of logic; that, for practical purposes, it matters little whether we have to deal with inheritance, or transmission through the germ-cells; that if the father has syphilis and the child is born with the disease, the fact stands evident that syphilis has passed from the elder to the younger generation; and most assuredly infectious diseases do thus pass. We think, however, that it must be admitted that there is some advantage in realizing with a certain amount of precision the course of events in such a process of infection—a certain advantage in the correct employment of terms—and assuredly the more we inquire into the data bearing upon the conveyance of tuberculosis or syphilis from the parents to their offspring, the more it is borne in upon us that even transmission by means of the germ-cells is most doubtful; the facts at our disposal best fit in with an antenatal, intra-uterine acquirement—an infection of the embryo or the fœtus at a later date.

Transmission of microörganisms by the egg is not unknown among lower forms of life. It may happen that the hen's egg is not perfectly sterile, and this in eggs that are freshly laid; the eggs of the silkworm may be infected by the organism of pebrine so that the developing caterpillars in their turn are found to exhibit the disease; similarly there is some evidence that the eggs of the tick *boöphilus* carry within them the *piroplasma*, the organism of Texas fever. Leaving aside the possibility in these last two cases that infection of the interior of the egg may occur at a late period, the germs being at first outside the egg-cases and only subsequently gaining entrance, it has to be pointed out that the eggs in all these cases are different from the human and mammalian ova. All the above have a relatively abundant yolk and food supply, in which the microbes may multiply without at first affecting the embryo. The human ovum, on the contrary, is devoid of yolk; the microbes, if present, would from the first be within the cells of the young embryo, and is it difficult to conceive such intra-cellular microbes lying inert; difficult to imagine that they would

not set up so serious a perversion of metabolism that if they did not rapidly destroy the embryo, at least they would induce developmental anomalies incompatible with eventual continued existence. Baumgarten and others believing in germinal infection have found it necessary to predicate a latency, or lying latent, of the pathogenic organisms. When we find that the post-natal tuberculosis of early infancy is characterized in general by a much more rapid infection and generalization than occur in the adult, the likelihood that at a yet earlier period the tubercle bacillus is arrested in its activities is at most extremely slight.¹

The observations of Schaudinn² upon trypanosomes (halteridium) and leukocytozoa (spirochaetes) of the stone-owl, may possibly oppose what is here said, for, according to him, both these forms of parasitic protozoön may make their way into the eggs of their hosts (mosquitos); and, as regards the former, he lays down that they rest during the development of the young gnat, becoming active when the latter is adult and begins to suck blood. In both these protozoön forms the conditions, so far as we may see, differ from what obtains with tubercle bacilli. In them we are dealing with species presenting a pronounced alteration of generations, and so accustomed to long periods of rest before circumstances are favorable for transmission to another host. In the absence of spores the existence of anything like a resting-stage in the tubercle bacillus is still regarded as doubtful, although, not to be partial, it has to be noted that certain modern authorities describe minute gonidial forms of the bacilli, and these might possess the property of latency. The saner view is that in man, the infection of the offspring from the mother is placental, and this view is supported by (1) the analogy of the acute exanthemata; (2) the absence of any constant stage of tuberculosis or syphilis manifested at birth; (3) the frequent evidence of placental infection; and (4) the general nature of the lesions in the offspring. Acute exanthemata attacking the mother in the last days of pregnancy can affect the child, which is born showing the acute lesions of the disease; here there can be no question of germinal infection. Infants may be born showing generalized and advanced syphilis or tuberculosis, or, on the contrary, may present indications only a week or more after birth: this very inconstancy indicates irregularity in the period of infection. Regarding the existence of infective lesions of the placenta we need say nothing here; no one denies their existence. Lastly, as regards the nature of the lesions, syphilis presents a specially instructive picture. In syphilis of postnatal acquirement the liver is infrequently involved; in 11,629 autopsies at St. George's Hospital, extending over forty-two years, J. L. Allen found only 37 cases of undoubted hepatic gummata, and 27 cases in which cicatrices alone were present. Flexner, including also cases of syphilitic fibrosis, found in Philadelphia altogether 88 cases of hepatic syphilis in 5,088 autopsies. In congenital³ syphilis the liver, of all internal

¹ Von Behring's recent theory that most tuberculosis in man is acquired in infancy from cow's milk, also demands a similar latency of the tubercle bacilli. The basis of this theory has been completely shattered by Kitasato's full statistical study of conditions in Japan. There tuberculosis at all ages is as common as in Europe and North America; but, in the first place, the native cattle are immune to tuberculosis; in the second, infants are not brought up on cow's milk.

² *Arb. a. d. Kaiserl. Gesundheitsamte*, Berlin, xx, 1904, pt. 3.

³ I have so far refrained from using this term, which, though strictly correct as

organs, is that most frequently involved. According to Chiari, out of 132 syphilitic infants examined, 119 showed hepatic involvement. This is scarce to be explained on the theory of germinal infection; it is exactly what we should expect from placental infection, and this because the blood of the umbilical vein passes first to the liver, which thus bears the brunt of the infection: it is here that the microbes of the disease are liable to be arrested. Yet another method of uterine infection, through the amnion and amniotic fluid, has also to be taken into account.

With reference to germinal infection through the spermatozoön and its unlikelihood, the following observations of Gärtner¹ deserve consideration.

As Wyssokowicz has demonstrated, the minimal number of tubercle bacilli which will set up peritoneal infection in the guinea-pig is eight. Gärtner, obtaining with every precaution the ejaculations from guinea-pigs rendered tuberculous by intra-tracheal injections, found that only five out of thirty-two ejaculations contained a sufficient number of bacilli to set up peritoneal tuberculosis in other guinea-pigs. Rohlf, taking semen from the bodies of men succumbing to pulmonary phthisis, did not once succeed in rendering rabbits tuberculous. (To set up peritoneal infection in the rabbit a minimum of twenty-four to thirty tubercle bacilli must be present.) From these and other considerations, Gärtner was led to the conclusion that the semen of the advanced phthisical patient, without direct tuberculosis of the genital organs, does not on the average contain as many as ten bacilli.

A careful computation of twenty-four cases has shown that the average human seminal ejaculation contains more than two hundred and twenty-six millions spermatozoa. (The number appears extraordinary, but is comprehensible when we remember that a cubic millimeter of blood contains five million erythrocytes.) Thus, says Gärtner, if the semen contained not ten but one hundred bacilli, the chances that an individual spermatozoön fertilizing an ovum should have with it a tubercle bacillus, and so cause germinal infection, are as 1 to 2,260,000. Even did the semen contain 1,000,000 bacilli the chances would be as 1 to 226. He pursues the argument further by showing that on the average only 1 out of about 85,000,000,000 spermatozoa has the chance of fertilizing an ovum. Suffice to say that the chance of germinal infection through the conveyance of tubercle bacilli by the spermatozoön is so absurdly minute that it must be neglected.

Infection of the offspring in utero by the father, when it occurs—as we know it does occasionally, and that without apparent infection of the mother—must happen at a later period, and two possibilities present themselves: namely, it is possible that there may be purely local infection of the womb, and more particularly of the placental area, from the seminal fluid of the male parent; or, without direct infection of the womb, there may, at a later period, be conveyance of pathogenic microbes from the uterine cavity through the amnion into the amniotic fluid. Without discussing these possibilities, it is here only necessary to state that it has been positively demonstrated that tubercle bacilli introduced

embracing the conditions of ante-natal disease, is so frequently regarded as synonymous with "hereditary" that to employ it is apt to confuse.

¹*Zeitschr f. Hygiene*, 13, 1893, 101.

into the uterine cavities of pregnant animals may later be detected in the amniotic sacs.

To repeat, we are forced to conclude that *specific injections are not inherited, but are of post-conceptual acquirement*. This, however, is not the same as stating that no inheritance of any order can occur in connection with specific diseases. To this latter possibility we shall return later.

CONDITIONS TRULY INHERITED.

We have now cleared the ground, and it may seem that very little of the nature of disease is left which can be inherited. Of actual disease, it is true, very little is left; of morbid conditions—of departures from the normal (variations), and morbid tendencies (diatheses),—much remains to be said: so much, indeed, that it is difficult to know where to stop; for to discuss these subjects adequately demands a study of the whole theory of inheritance.

But first, in order to think clearly over these matters, it is well to treat apart as far as possible two broad groups of cases; namely, the cases in which we have to deal with the inheritance of conditions which have passed down from earlier generations (and dealing with that we will for the time leave out of consideration how these departures from the normal gained origin); and, secondly, those cases in which abnormal conditions have manifested themselves first in one or other parent. It is when discussing these that, to gain a grasp of their meaning and extent, we shall have to inquire into their origin and strive to establish an adequate theory of inheritance. We arrive at the same result by classifying the truly inherited morbid conditions into: (1) *Ex specie*, or specific; (2) racial; (3) familial; and (4) individual. We may rapidly run over examples of the first three classes; it is the fourth that we shall have specially to study.

1. *Ex Specie*.—The fixity with which specific properties are inherited, as compared with familial or even racial peculiarities, affords the most patent example of the working of the law that those features which have for the longest period been possessed by a given stock are the features most impressed on that stock, and least easily lost. It is in the broad study of species that the existence of heredity is most emphasized. Conditions which, we must assume, had originated as variations or as mutations have ceased to be pathological and have become attributes of the species. In the majority of these specific variations we have to see a definite advantage; following the present trend of evolutionary thought we recognize an inherent probability that it is those features of advantage to the stock that are retained, while valueless variations tend to disappear. Bland Sutton has suggested that this is not always the case; that a useless variation in one part of the organism may show itself along with a variation of advantage in another part, and, being coincident, both may tend to be perpetuated. He cites the “castors” situated on the inner side of either foreleg of the horse—horny cutaneous overgrowths unconnected with the bone. The only suggestion that he can make is that these have shown themselves primarily as a correlated variation along with others more valuable in some prepotent ancestor. Another remarkable example,

apparently of this class, is seen in that strange fish, the chaetodon, with its osteomatoid enlargements of sundry bones.

There are more easily recognized functional morbid inheritances. Notably, the different species show strongly defined differences in susceptibility to various diseases. Thus each species harbors one or more forms of the grosser parasites which are peculiar to it, and the same may largely be said with regard to microbic parasites. We need but suggest that typhoid, gonorrhœa and syphilis appear, under natural conditions, to be limited to the human species.

2. Racial.—Dealing with races we observe numerous minor anatomical varieties, nor can we in every case comprehend their development, save as “sports” which have appeared in some ancestor of the race and have been perpetuated. Without going far afield abundant examples may be called to mind: the lack of development of the nasal bones in pug dogs; the existence of horned and hornless races of domestic cattle; the absence of tails in certain races of sheep and cats, etc.; while, coming to man himself, we observe pronounced differences in the quality of the hair and the pigmentation of the skin of the different races, not to mention deeper structural peculiarities such as the symmetrical exostoses of the malar bones among the Akim (or horned men) of Africa, and the penile bone present in yet other African races. There are among the different races of animals, as of man, different susceptibilities to infectious diseases. The native cattle of Japan, as again the “Buffel” or native cattle of Austro-Hungary, are relatively insusceptible to tuberculosis; a race of Algerian sheep shows a similar relative insusceptibility to anthrax, whereas sheep in general are highly susceptible. As between human races these differences in susceptibility are well marked. We need but cite the relative susceptibility of Melanesians to measles, of Negroes to tuberculosis, of Malaysians and other oriental races to beri-beri, of those of European descent to yellow fever.

3. Familial.—Taking man alone into consideration the instances of familial inheritance of abnormal conditions are so numerous that it is impossible within the limits of this article to attempt anything approaching a complete record. As we have indicated elsewhere, they may roughly be divided into:

(A). **Gross Anomalies.**—There are abundant instances of the inheritance by successive generations of one family of such conditions as polydactyly, syndactyly, abnormal shortness of one or more phalanges, hypospadias, phimosis, etc. So marked, indeed, is this inheritance that there is recognized a tendency for those possessing such anomalies to be prepotent; *i. e.*, the majority of the progeny of these individuals mated with more normal individuals exhibit the like anomaly, whether in the one sex only or in both.

(B). **Probable Anomalies of Defect.**—Such are hæmophilia (exhibited more particularly in the males, but descending through the female line), albinism, Daltonism, myopia, strabismus, ichthyosis.

(C). **Susceptibility to Specific Infections.**—Certain families are notoriously more prone to certain infections than is the generality of the community. This is especially marked in connection with tuberculosis, and this when due deductions are made for house infection, subjection to similar environment, etc. We recognize, in short, a tuberculous dia-

thesis. In other families the exanthemata, such as measles and scarlet fever, are specially apt to take a severe form.

(D). **Diathetic.**—Other conditions, due, it would seem, to disturbances of metabolism, underlying which may very possibly be finer anatomical variations, have for long been noted as tending to be inherited; such are obesity, diabetes, gout, and chronic rheumatism (though all of them assume also a racial aspect). Upon further consideration it will be seen that this and the preceding class are doubtfully to be separated; the essential feature common to both is an inherited habit of body or vice of organization—a constitutional weakness in one or the other direction. In all these cases we are apt to observe a form of “homochronous inheritance;” *i. e.*, the disturbance is apt to manifest itself at or about the same life-period in the offspring as in the parent.

(E). **Nervous.**—More and more attention has been paid of late years to familial nervous disturbances, of which two groups may be recognized, the *homeomorphic* and the *heteromorphic*. In the former the offspring show the same lesions and symptoms as did the parent. These are cases more particularly of lack of development or premature atrophy of certain groups of nerve-cells, and among them are to be included familial palsies, pseudohypertrophic and amyotrophic paralyses, Friedreich’s disease, Thomsen’s disease, etc. It is noteworthy that the more these conditions are being studied, the greater is the number of strictly localized familial diseases that is being determined, each group affording a particular syndrome.

The heteromorphic disturbances embrace a series of cases in which, the parent suffering from one form of nervous disease, the progeny may individually exhibit one or more of a group of other nervous disturbances. Broadly speaking, it would seem that here we have to deal not so much with lack of development and atrophy of particular groups of nerve-cells as with lack of the highest development of the higher centres as a whole; there is wanting perfect stability and coördination of various parts, so that according to the strains to which the individual members of the family are subjected, now one, now the other series of centres may show itself unable to respond adequately, and one or other form of mental disturbance and nervous disease may result. Here are to be included conditions of insanity, familial epilepsy, hysteria, and the neuroses.

INDIVIDUAL INHERITANCE.

Strictly speaking, every property possessed by the individual which is not, or cannot be, ascribed to intra-uterine influences and postnatal acquirement, is the individual inheritance. It has reached him through the parental germ-plasm; thus, specific, racial, and familial traits become the individual property. For practical purposes, however, all of these may for the moment be neglected, and merely those properties taken into consideration which, (1) peculiar to the parents as distinct from the family, reappear in the progeny; or, (2) not observable in either parent or parental stock, can only be ascribed to the interaction of the two parental germ-plasms. We have here, in short, to deal with *variation*, whether

first appearing in the parent or in the offspring, and must of necessity inquire into the factors bringing about individual variation.

This inevitably demands an inquiry whether conditions acquired by the parent can be transmitted to the offspring. We approach the crucial point of the whole debate. If influences telling on the parent modify the constitution of the offspring, then not merely do we gain an insight into the ultimate causation of individual variation, and, what is more, an insight into the meaning of the evolution of the species, but also to some extent approach the Lamarckian standpoint. I say "approach" because the full Lamarckian doctrine demands that the identical change acquired by the parent become transmitted—that if, for example, the giraffe by straining towards higher things adds a cubit to his stature, the little giraffe is born with larger forelegs and longer neck than are possessed by his cousins. What we have said regarding the non-inheritance of mutilations will have indicated that we cannot see how this extreme doctrine is to be accepted.

We must deny the inheritance of acquired gross structural modifications, and if this is the essence of Lamarckianism, then Lamarckianism we cannot entertain. What we here refer to is the possibility that the molecular constitution of the germ-plasm may be modified in one or other direction by influences acting upon the parental organism, with the result that the offspring varies in one or other direction according to the nature of this influence. Variations so produced would not be identical with the modification acquired by the parent, but might be specific to this extent, that a given influence acting on the parent would tend to variation in the offspring along certain definite lines. If this is found not to be the case there is but the alternative that each parent hands down to the offspring a fixed germ-plasm; that the molecules constituting this germ-plasm in the ovum and spermatozoön respectively are not of identical composition and arrangement; and that consequently it is to the *amphimixis* or commingling and interaction of the two unlike parental germ-plasms that variations are due. According to this view the laws governing variation are akin to the laws determining the pictures presented by the pieces of glass in the kaleidoscope.

It may seem that here we approach matters too intricate for solution—matters altogether too deep and removed from medical practice to require treatment in a work of this nature. And yet a little thought will show that for medical men here also is the crux. Upon our answer to this question depends, if not our whole outlook over the inheritance of disease, at least our attitude towards the one problem of heredity regarding which our advice is most often sought. If the germ-plasm is fixed and variation is due simply to amphimixis, then disease in the father should have no effect upon his children, save and except that disease be conveyed by him to the mother and so tell upon the intra-uterine nutrition of the foetus; or, more remotely, be conveyed by him to these children after birth. If, on the contrary, parental disease not directly affecting the ovaries or testes can nevertheless, by the toxins generated elsewhere and circulating in the blood, deleteriously influence and modify the nuclear material of the ovum or spermatozoön, just as it may modify the other cells of the body and their nuclear material, then, obviously, the molecular constitution of the individual developed from the germ-cell must vary from the normal; or

otherwise parental disease is liable to affect the offspring very materially. It will be seen that everything leads me to accept the latter view. It will, however, aid our understanding of the problems presented if first we endeavor to classify individual variations and collect certain data bearing upon individual inheritance in general.

The Different Forms of Individual Inheritance.—As regards any one property, structural, constitutional, or mental, the individual may exhibit the following forms of individual heredity:

1. Inheritance to an Extent Intermediate Between What Has Obtained in the Parents.—The *blended* is the commonest type of inheritance, and would seem to indicate an equality of influence on the part of the respective germ-plasms. The broad tendency of sexual conjugation is to preserve the mean and perpetuate the type, rather than to induce extreme varieties and develop new species.

2. Mosaic Inheritance.—This form is rarely to be made out distinctly. It may well be more frequently in action than we can recognize. It is best exhibited in cases of piebald animals, the offspring of parents of different colors. Here the two colors do not blend in the offspring, but both are represented independently in different areas. It is thus a form of particulate inheritance though not of exclusive.

3. Reproduction of the Condition Found in the One Parent to the Exclusion of That Seen in the Other.—This form of *particulate* inheritance is specially noted in connection with certain properties. Thus where one parent has blue eyes, the other dark brown, the children have either blue or brown eyes, rarely those of an intermediate color. What is more, as shown well by Mendel in his studies upon hybridization, and fully confirmed by numerous biologists during the last few years, while in general the properties of the hybrid are apt to be intermediate between those of the two parents, certain properties are apt to be *dominant*. The "hybrid character" resembles that of one of the parental forms so closely that the other either escapes observation completely or cannot be detected with certainty. But the character not exhibited by the hybrid is not of necessity entirely lost—only *recessive*. In studying plant hybrids, which manifest this exclusive inheritance, as the result of self-fertilization of the hybrids, the recessive character has been found to reappear in a certain definite proportion of the plants of the next generation. Growing these hybrids and their offspring, (the result in each case after the first of self-fertilization,) it has been found that each plant presenting the hybrid characters may give, *as regards any one pair of exclusive characters in the original species* (length or shortness of stem, inflated or constricted seed-pods, axial or terminal flowers, etc.), a remarkably definite proportion of offspring. If D be the dominant and R the recessive character, the proportion of forms produced from the hybrid parents is expressed by the formula: $(DD + 2D[R]^1 + RR.)$

Two hybrids, though of the dominant type, are produced to any one plant that has the dominant character fixed and every one that has the recessive character fixed. Henceforth plants of the pure D type will by self-fertilization produce only offspring of that type, with no reversion

¹ Following Castle, we place the R¹ in brackets to indicate that the recessive character, while possessed by the germ-cells, does not show itself in the individual. To external appearance the progeny consists of 3D + R.

to the R features; and so with parents possessing the R character. The hybrids D [R], however, in each subsequent generation produce the definite proportion of dominants, hybrids, and recessives.

When the species differ in several pairs of features, the result, though following the same lines as regards each individual pair, becomes much more complicated, although eventually, after several generations, individuals of the pure parent types are reproduced. In other words, by this exclusive inheritance the results of a *mésalliance* in the pedigree may be completely cast out and the stock become once more pure. Castle and Allen have demonstrated the existence of the same law in animals—mice—in regard to coat color.

4. Production of New Features and a New Strain by Cross-Breeding.—There is shown, it may be added, an equal likelihood that the mating of two individuals which, as regards two pairs of contrasted characters (or *allelomorphs*), exhibit each reversely a dominant feature as regards the one and a recessive as regards the other will result in the development of definite proportions of individuals resembling neither stock but showing a commingling of two dominant or two recessive features. If either of these new forms be mated strictly with other individuals of the same type there results a *new strain or variety* breeding true and distinct from either ancestral stock. Thus, to quote Bateson, if a red variety of some plant, say a stock, be crossed with a cream-colored variety, while the hybrids of the first generation are red (red being dominant), in the second generation a small proportion (three-sixteenths of the total progeny) of plants may appear with flowers neither yellow nor red but *white*, and these white-flowered forms, if crossed among themselves or allowed to undergo self-fertilization, yield a permanent white strain. The explanation here is that the one ancestral form has red sap (D) with colorless corpuscles (R) floating in it, the other, colorless sap (R) with cream-colored corpuscles (D). In this way some of the second generation come to possess a mingling of the characters, colorless corpuscles and colorless sap. This, it may be noted, is the basal principle underlying the production of new strains or varieties by the horticulturist and undoubtedly helps to explain the production of one order of the “sports” to which we refer in a later paragraph. Interesting as it is, we shall not here enter into a detailed account of the Mendelian doctrine, which has provided keen activity of late, more particularly among English and American biologists; to discuss it adequately would demand many pages. A consideration of its bearings upon the inheritance of morbid conditions is given by Bateson, the leader of the school, in a lecture to the Neurological Society of London.¹

In the human race, where not only there is no self-fertilizing but conjugation between those of the same stock is largely prohibited, and where, again, the number of points of difference between the individuals is extraordinarily great, Mendel's law can rarely be brought to apply, save in the most general terms. In any case it does not explain, any more than does the law of gravitation. It helps us, however, to harmonize data otherwise not a little confusing—to recognize dominant features in the members of a family (such as, for example, the well-known Hapsburg

¹ *British Medical Journal*, 1906, ii, 61

lip), the appearance of recessive features in a certain number of the members of a later generation, etc. When in gout and hæmophilia a given diathesis skips a generation we realize that we are dealing not with isolated phenomena but with conditions subservient to law. Where one parent has a neurotic or alcoholic heredity we realize that it is not essential that all of the progeny be neurotic or show stigmata of degeneration, though at the same time we are bound to realize that while the parents themselves may show no vice of organization, yet, if either comes from an unsound stock, there is the possibility that in them the particular inheritance of morbid state is merely in abeyance (recessive)—that it may show itself once more in some of their offspring. There is the lesser possibility that by fortunate mating it may be wholly cast out not to reappear. In these instances we are dealing with true *atavism* (*atavus*, a grand-father), or—

5. Reproduction of a Condition Seen in Generations Nearly Preceding the Parental.

6. Reversion.—The reproduction of remote ancestral conditions. Atavism must, we hold, be regarded as distinct from the next condition which may show itself, namely, *reversion*. In atavism there is no necessary degeneration; the return may be to a better type. By reversion is meant at least loss of properties common to the stock or race and the reproduction of the characteristics of the lower type in the line of descent. If ontogeny be an abbreviated phylogeny, then by reversion we understand the development of the individual up to some point short of the completed phylogeny.

This again is well exemplified by certain studies in hybridism. Some of the latest are those of von Guaita,¹ who found that breeding together a tame albino mouse with a piebald Japanese waltzing mouse the progeny was a "wild gray mouse." The color and general configuration here were not those of either parent: they were those of the presumptive wild ancestor from which both strains had their origin long generations previously. Even more remarkable is Darwin's famous case.² The ancestors of our domestic pigeons were probably eastern birds; it is known that for now some centuries the leading varieties have been bred in Europe, for still longer centuries in India and the East; and everything indicates that their ancestors were the wild blue-rock pigeon (*Columba livia*). Crossing a barb-fantail female with a barb-spot male, Darwin produced a bird "which was hardly distinguishable from the wild Shetland species" (of blue-rock). Weismann has supposed that in Darwin's case the similarity was purely in the color and the bars on the wings. Ewart,³ crossing an absolutely white fantail with thirty feathers in its tail with an owl-archangel hybrid, (the owl was powdered blue, with a short beak; the archangel copper-colored, with well-developed crest) obtained a bird which in measurement was almost identical with the blue-rock, while in color and markings it showed complete reversion to the checkered blue-rock of India, and, like that, had only twelve tail-feathers.

In this "harking back" we seem to have what may be termed a "greatest-common-measure" action. In this fusion of the germ-plasms

¹ *Bericht d. Naturf. Gesamml.*, Freiburg 10, 1898, 317; and 11, 1900, 131.

² *Animals and Plants Under Domestication*, I., p. 204.

³ *The Penguik Experiments*, 1899, p. xxvi.

those "constituents," if we may so express it for the moment, which had controlled the racial differences in the respective parents antagonize one another, and the older constituents common to the two germ-plasms alone control the development of the offspring.¹

Such a cutting off, or inactivity, is liable to occur generally when widely separated stocks are mated—until the point is reached when no result is obtained, the union being sterile. The cutting off is of the recessive type and not absolute, for later generations may furnish individuals returning again to either primary parental type. DeVries nevertheless lays down that Mendel's law does not hold satisfactorily in connection with other racial properties.

7. Degeneration and Degenerates.—Herein we have a condition allied in its results to the reversion just described, but differing in this, that the parents belong to the same stock. Although in externals they may or may not appear to be normal, their offspring are of low type, the cranial capacity less than normal and reversionary in character, and, more particularly, the intellectual and moral properties approximate toward those of the uncivilized and lower types of mankind. We shall have later to discuss the causes of such degeneration. Here I would only state that under this heading must be included certain less-pronounced conditions of defect—conditions in which it may be that only one system, notably the nervous system, shows signs of defective development; or, again, in which no positive structural defect may be made out, but the constitution is feeble and the natural resistance to disease possessed by the race is characteristically lowered.

8. Excess of Development of a Property Over What Obtains in Either Parent.—Mendel noted forty years ago that in hybridization the cross-fertilization of a tall-stemmed (4 to 5 foot) variety or species of pea with a short-stemmed species ($1\frac{1}{2}$ to 2 feet), regularly led to the production of hybrids taller (6 to 7 feet) than the taller parents. Within certain limits the cross-fertilization of distinct stocks leads to progeny exhibiting greater vigor of growth than either parent. It is a familiar observation in Canada that the offspring of mixed Anglo-Saxon and French marriages tend to be of better build, brighter, and more active, than the rest of the community whether French or Anglo-Saxon. The same was noted of the Normans centuries ago.

9. Sports.—Mutations.—The abrupt appearance of conditions neither parental nor ancestral.

Certain gross anomalies are clearly reversionary; although appearing abruptly in the line of descent, they reproduce obviously organs or parts well developed in some ancestor. Such for example are various persistent ducts and cysts developing along the course of such ducts—the majority of the cardiac anomalies, cleft palate, supernumerary nipples, etc. The list can be greatly extended, although, as will be noted later, it is not always possible to distinguish between the inherited and the acquired conditions of this order; by which we mean that everything points to the fact that a considerable number of anomalies are due to influences acting on the embryo. Wholly apart from these is another series of appearances.

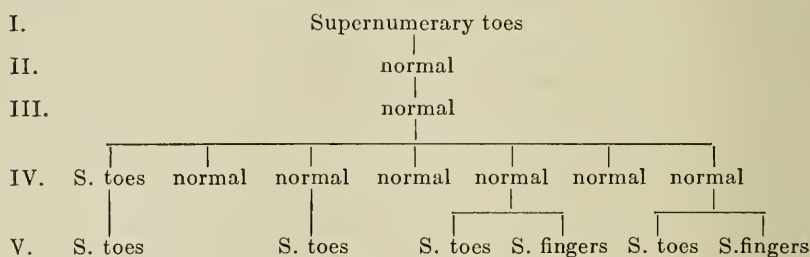
¹This explanation of "harking back" appears to possess greater inherent probability than Bateson's "meeting of two complementary elements which have somehow been separated by variation."

Once again to take a botanical example: in a bed of single tulips a rare flower-head may show only five petals; another may show seven. The liliaceæ, to which the tulips belong, are throughout characteristically six partite, and if one of these variations is reversionary to an ancestral condition, the other cannot be. From the fact that in neither case is the general character of the tulip greatly altered, the probability is that neither condition represents a reversion, and that both are *sports*. The four-leaved shamrock is of the same order. We owe to the great Belgian botanist de Vries the fullest study and recognition of this production of 'mutations.'¹ Cultivating the plant *Oenothera Lamarckiana* over a long series of years—in fact since 1886—he observed the appearance from time to time of individuals which definitely varied from the parents, and, what is more, when fertile, were true to seed. Thus in 1895, to quote an instance, there appeared the relatively huge *Oenothera gigas*, and that not by gradual variation but by a sudden jump. Subjected to self-fertilization this single plant afforded seeds giving origin to plants (several hundreds) of the *gigas* type. At a bound therefore a new species was seen to develop. As de Vries points out, we have here an example of discontinuous and not of gradual evolution, and he holds that in all cases evolution must be of this discontinuous type. In this as supporting a physico-chemical theory of inheritance we cannot but agree with him. To quote Jacques Loeb,² "If the (determinants) are comparable to a series of compounds, *e. g.*, of alcohols, there is no more a transition possible between two species separated by a difference in only one determinant than there is a transition possible between two neighbouring alcohols of the same series." We meet with similar conditions in animals. Thus it is known that the celebrated royal strain of cream-white horses at Hanover originated by careful inbreeding from a single sport—a white horse which appeared fortuitously in a breed that had previously shown no tendency to throw white horses. Certain breeds of merino sheep are also traceable back to a single sport possessing silky hair in place of the ordinary wool; and so on. In man we occasionally encounter the same, though it has to be admitted that well-authenticated family histories are rare, and we cannot always assure ourselves that a given sport has appeared in a given family for the first time; *i. e.*, that it is not an inheritance. The most frequent examples are what Bateson has called meristic—alterations in the number of parts in series. Such are increase or diminution in the number of the teeth, vertebræ, ribs, fingers, toes, etc. It is difficult to speak with precision of internal organs, but probably some cases at least of double kidneys and ureters, accessory ovaries and testicles, etc., come under this group. In addition there are what may be termed metabolic sports—conditions of albinism, ichthyosis, etc. It is common to class most of the examples of the first, meristic, class as instances of reversion; but the more one studies them the more evident it is that they must in general be included as sports. They occur most often in those who present no other signs of reversion, and, as already stated, if numerical increase is an instance of reversion, numerical decrease cannot be; and *vice versa*. Supernumerary digits crop up in no

¹ *Die Mutationstheorie*, 1901.

² *The Dynamics of Living Matter*, New York; MacMillan, 1906, 225.

particular position; they may show themselves at either end of the series, or as a reduplication of the index or the middle finger. When a supernumerary mammary gland appears in the line between the outer end of the clavicle and the pubic symphysis (the line along which the mammary glands are arranged in animals possessing multiple pairs), there is some force in the argument that they are reversionary, although it has not been shown what direct ancestors of man possessed multiple mammae. When, as occasionally happens, the supernumerary gland occurs on the shoulder or the hip, to speak of reversion is absurd; this can only be a sport. What is very marked is that sports as a rule are curiously dominant; once they appear they may reappear through several generations; they may skip one or more generations; they may affect alternate generations. Hey¹ has afforded a good instance of this recently, in which the existence of supernumerary digits was first noted in the great-grandfather, was absent in the next two generations, affected one of the seven children of the grandfather, and affected six children, the offspring of three of the above seven. Whereas in the earlier generations the toes were affected, in the last, in some individuals the toes, in others the fingers, were supernumerary.



It is almost needless to call attention to the pronounced inheritance, often alternate, of albinism and hæmophilia, which may both be placed in the category of metabolic sports.

If now we attempt to sum up the various forms of individual inheritance brought about by fusion of the germ-plasms of the two parents we make out the following points:

I. Inheritance of a property or group of properties may be either blended or particulate.

II. There are various grades of *blended* inheritance:

(a) *Intermediate*, the commonest, with on the one hand the sub-groups:

(b) *Cumulative*, the blend producing a quality superior to that possessed by either parent.

(c) *Progressive sport production* (sports of excess), the blend inducing additional properties in the offspring not possessed by either parent.

And on the other hand—

(d) *Antagonistic*, certain properties in the two germ-plasms antagonizing one another and leading the offspring to have qualities inferior to those possessed by

¹Hey: *British Medical Journal*, May 28, 1904.

either parent, and so to revert toward an earlier stage in the ontogeny or phylogeny. We can distinguish the following varieties:

Atavistic.

Reversionary.

(e) *Regressive sport production* (sports of defect), the blend leading to defects not to be explained by phylogenetic considerations.

III. With regard to *particulate* inheritance this may well be only a particular case of what we have termed antagonistic blended inheritance. For the present it is perhaps well to treat it as distinct. It may be either—

(a) *Mosaic*—One property in which the two parental stocks differ being conveyed to and effective in the germ-plasm from which the offspring originates so that in part the offspring exhibits the dominance of the property conveyed from the one parent, in part the property conveyed from the other.

(b) *Dominant*—The germ-plasm of the one parent dominating the offspring as regards one or more properties; that of the other not being wholly neutralized but merely recessive, being contributed also to the germ-plasm of the offspring so that in its turn the property may reappear in a later generation.

(c) *Exclusive*—Certain “constituents” of the germ-plasm of the one parent wholly replacing or casting out the corresponding constituents of the other, so that the peculiar features of that other parent are not reproduced in any subsequent generation.

Are all these various forms of inheritance the results of chance combinations of the constituents of the maternal and paternal germ-plasms, or can we discern certain underlying laws? It is clear that we are not dealing with mere chance, even though chance also has its law. Certain phenomena appear with such regularity (when large series are taken into consideration) that clearly they have laws specially influencing them. One of these laws I have already indicated; namely, that of Mendel on cross-breeding. There are still those biologists who attack it; but the more it is studied the more cases are found to harmonize therewith. This bears on particulate heredity, and it may well be that the apparent exceptions are cases of other phases of what above I have termed “antagonistic blended inheritance.” Bearing more particularly upon blended inheritance we have another law, that of Francis Galton, recently modified by Karl Pearson. The latter unfortunately has not troubled to translate his law out of an algebraic equation into English,¹ and so the ordinary reader would be unable to follow it. Pearson accepts Galton’s general principle but holds that the terms of the series are different, the contribution of the different generations being greater than held by Galton. Herein our own line of argument leads us to believe that he is right. For general purposes, however, Galton’s law is near enough for purposes of expression. It is that the two parents contribute one-half (or each one-quarter), the four grandparents one-quarter (or each one-sixteenth), and so on. The series $\frac{1}{2} + \frac{1}{4} + \frac{1}{8} + \frac{1}{16}$, etc. = 1; i. e., equals the total inheritance.

THEORIES OF INHERITANCE.

Based upon and deduced from the study of long series of cases these laws are of distinct value. They do not, however, explain what is the nature of heredity that these laws should be in action. In seeking to answer

¹ The formula is discussed in Pearson’s *Grammar of Science* (2d edit.), London: 1900.

this we immediately proceed into the realm of hypothesis. There have of late years been abundant theories brought forward, but none has attracted greater attention than that of Weismann, none has been so fully worked out; and as the distinguished author of the theory in the evening of his life has given us this theory in a rounded and complete form which has, further, been admirably translated,¹ it will be well to take this as a basis.

Weismann accepts, as indeed he was one of the first to emphasize, that inheritance is conveyed by germ-cells which have from the first been set apart for reproductive purposes. These germ-cells as such take no part in the building up of the parental individual of whose organism they form a part; only when liberated and fertilized do they proceed to multiply, giving rise to one set of cells which form the body as a whole, and to another smaller set—the germ-cells. In other words, he holds that the germ-cells contain within them two constituents, the somatic- or body-plasm and the germ-plasm. The tissues built up by the somatic-plasm are mortal, subject to death; the germ-plasm is potentially eternal—it is carried onward from generation to generation. Here is the first weak point in Weismann's argument—a false conception which vitiates the whole subsequent train of thought. The germ-plasm is not potentially eternal. If, as already indicated, the individual human being derived from a solitary spermatozoön and a solitary ovum can produce on the average, as already indicated, 85,000,000,000 other spermatozoa each resembling the primordial spermatozoön in size and properties, it is clear that—leaving the body-cells out of account—the germ-plasm contained in that primordial spermatozoön has multiplied itself several thousands of millions of times; or otherwise it has in the process of growth assimilated vast quantities of other material to itself, and rearranged it so that that new material has come to possess the same constitution, and, with this, the same properties as itself. With growth there is constant new formation of molecules forming the individual cells. In other words, the germ-plasm is not eternal; it is constantly being renewed. *What are the nearest to being potentially eternal are the chemical and physical properties of the germ-plasm;* and this very fact, that growth implies constant rearrangement and assimilation of constituent molecules, makes the chemical composition "eternal" only so long as the assimilable material remains the same. To this I shall revert. Weismann, it is true, admits that there is growth; he does not, however, realize all that this necessitates.

He next demonstrates very clearly that this heritable germ-plasm is contained in the nuclei of the conjugating ovum and spermatozoön, (*vide* p. 18), and regards as a proved proposition that the nuclear chromatin is the hereditary substance. This is present in the germ-cells of every species in the form of a definite number of chromosomes which, in cells destined for fertilization, is reduced to one-half the number; so that the single nucleus—the segmentation nucleus—of the *fertilized* ovum contains the number of chromosomes characteristic of the cells of the individual of any particular species. The hereditary substance of the child is therefore formed half from the maternal, half from the paternal substance, and as, at each succeeding cell-division, each of the paternal and

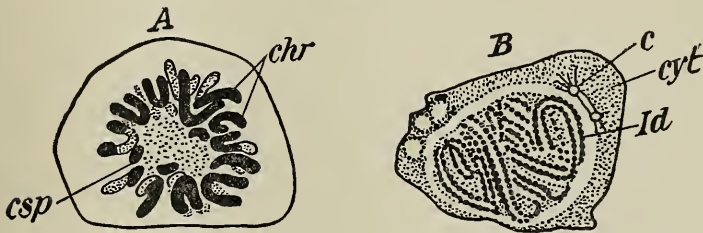
¹ August Weismann: *The Evolution Theory*; translated by J. Arthur Thomson and Margaret R. Thomson. London Ed., Arnold: 1904.

maternal chromosomes doubles by dividing, each cell of the individual contains hereditary material derived from both father and mother.

This very fact of reduction, he points out, indicates that half the chromosomes contain all the essential primary hereditary constituents, or, otherwise, that it is not the chromatin as a whole that conveys hereditary properties. The rather, this must be made up of a series of constituents or *ids*, each of which is representative and capable of conveying all the paternal or maternal properties.

Let us pass back a generation. The germ-cells of the parent are similarly formed by a combination of chromosomes from the two grandparents. These must be represented, as indeed must also be the chromosomes of the great-grandparents, etc. What is more, in the process of reduction he holds that certain chromosomes derived from certain ancestors are cast out, others retained, and that it is the variation in the series of retained chromosomes that in the main determines the variations between the members of the same generation. The hereditary substance in the fertilized ovum thus consists of several complexes of primary constituents contained in the chromosomes, or "idants," each of which complexes (an "id") comprises within itself all the primary constituents of a complete individual.

FIG. 1.



Each "id" Weismann conceives as being composed of a mass of different kinds of parts, each of which bears a relation to a particular part of the perfect animal, and so to some extent represents its primary constituents, although there may be no resemblance between these "Anlagen" and the finished parts. These representatives of individual parts contained in each "id" he terms "determinants" (Bestimmungsstücke). In each "id," therefore, there must be as many determinants as there are regions in the fully formed organism capable of independent and transmissible variation at all stages of development—for the caterpillar stage, for example, as well as for the butterfly; determinants even for the egg, because eggs, caterpillars and butterflies are seen to vary independently. If, as has been noted, the individual hairs on the antennæ of insects are capable of transmissible variation, and if, in man, the conformation of particular teeth is inheritable, then determinants there must be for these individual hairs and teeth. If a little patch of scales on the butterfly's wing is peculiar to one variety, for those few scales there must be a determinant.

And lastly, each individual determinant must be made up of molecules of living matter, or *biophores*. Such biophores, he holds, must be larger than any chemical molecule; they must consist of groups of molecules,

some large and complete, others simpler and more minute; so that ultimately it is the interaction of these biophores—the casting out of some from one parental stock, the retention of others in their containing determinants and ids—that determines variation. No two individuals contain identical groups of determinants and identical ids, and, as these control development, therefore no two individuals are identical. If in reversion the characters of an ancestral form, it may be hundreds of generations back, are reproduced, this is because in the process of reduction, followed by fusion, of the two parental germ-plasms, the ancestral ids come to predominate to the exclusion or casting out of the ids of more recent generations. Why this should tend to happen in a special order of cases the theory does not venture to explain.

The reader from these data should be able to apply the theory to particular cases. It has also to be added that Weismann holds that the development of the individual from the ovum proceeds in such a way that by nuclear division it is brought about that the germ-cells are assured of possessing a complete set of ids, whereas the body-cells do not gain this complete set. There is a qualitative differentiation of the chromatin passing to what are to be the eventual tissues of one or other order, so that ultimately the particular determinants find themselves in control of particular groups of cells, destined to produce specific tissues or parts of tissues.

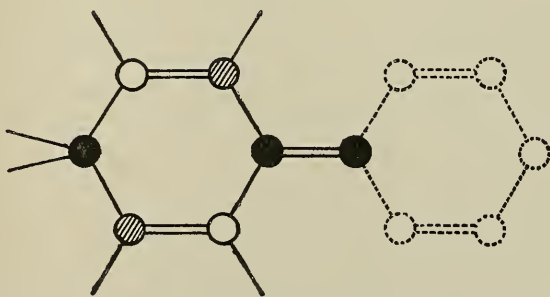
There is, we confess, something that savors of medieval scholasticism in this conception,—something remote from our general conception of the order of natural events, and, as a matter of fact, the whole edifice of ids, determinants and biophores collapses when confronted with the findings of physical science. Weismann's biophores, in brief, composed as he imagines them of numerous molecules, some of them complex and of large size, must be smaller than are individual atoms! We can in certain nuclei recognize rows of granules forming the individual chromosomes—little bodies $0.5\ \mu$ or less in diameter,—bodies considerably smaller than the micrococci of suppuration. These Weismann regards as the individual ids. Each id is, he postulates, made up of determinants, of which, as each region capable of variation is supposed to be represented by a separate determinant, there must in the human id be thousands rather than hundreds. Each determinant is made up of biophores or ultimate units of living matter; each biophore, according to him, consists of a group of molecules. Each molecule is, we may add, composed of numerous atoms. Now Lord Kelvin, in his convincing investigation into the size of the molecule of water (by a study of the thinnest possible films of a bubble), has proved that in a line $0.5\ \mu$ in length there could be only about 150 molecules of water. Let us be generous and compute the ids as being not on the average 0.5 but $1.0\ \mu$ in diameter, and, again being generous, let us compute the ultimate molecule of living matter as being only thirty times the size of the molecule of water—from every consideration an absurd underestimate. It will be seen upon calculation that the id (supposing it to be spherical) can contain only about as many molecules as presumably Weismann requires for one or two biophores, or at the most economical rate for a single representative determinant; and not one, or two, or three, but several hundreds of determinants, ought to be compressed into a respectable id.

We have, in short, the *reductio ad absurdum* of Weismann's theory. But if "idants," "ids" and "determinants" be swept away and we accept the existence of biophoric molecules—of individual molecules of living-matter;¹—if, that is, we very largely dismiss the latter part of the theory, and, in place of this purely morphological conception of heredity, build upon a chemical basis, we can safely utilize much of Weismann's super-structure of carefully collected facts and develop a theory which satisfies. And it is the work accomplished of recent years by the pathologist, the bacteriologist, and the physiological chemist, that indicates the lines such a theory must take. Space forbids that in these pages, that theory be fully developed. We can but indicate its broad outlines.

A Physico-Chemical Theory of Inheritance.—1. The studies of the physiologist and physiological chemist abundantly indicate that all vital activities are ultimately the expression of molecular rearrangements and combinations. Life is therefore the expression of a series of chemical changes, and the material endowed with life must be of such a nature that it, itself, is composed of molecules which react.

2. So many are the vital reactions even of the simplest microorganisms known to us that, employing current chemico-physical concepts, we must regard the individual molecule endowed with vital properties—the biophore (to utilize Weismann's term)—as of relatively great size and complexity. We best conceive it as a central ring, resembling the benzol ring, of associated carbon-containing molecules of which each member has side-chains capable of being satisfied, the peculiar feature of the vital system being that as a whole it is never satisfied and so is constantly interacting, and has the capacity to act upon and be acted upon by the surrounding medium. When the unsatisfied molecules forming a side-chain attach to themselves other atoms or radicals from the sur-

FIG. 2.



rounding medium and become satisfied, they tend to form an independent simpler system, which breaks off, leaving once more an unsatisfied affinity in the main system, and so long as the surrounding medium is otherwise

¹ It will be seen that our conception of the biophore differs a little from that of Weismann. We regard it as the unit molecule of living matter; Weismann makes it his unit of living matter but composed of several molecules. We employ this self-explanatory term rather than commit the crime of adding one more name to the long list of those intended to convey what is practically the same idea.

unaltered, similar atoms or radicals are once more attracted or attached, and the process is repeated.

3. The dominant vital activity is *growth* or increase in the amount of living matter; all the other properties of living matter lead up to and subserve this. With the conception above stated of the nature of living matter we are forced to recognize that growth is brought about by a process of satisfaction of side-chains in such a way that in connection with any given biophoric molecule there is attracted and built up an arrangement of atoms and radicals identical with those of the central ring, which, when completed, breaks off as above indicated. The accompanying figure (on page 39) diagrammatically represents the process here suggested.

Having the same structure, this newly formed molecule must possess the same properties. In other words, by such a process of identical aggregation we can conceive the development of two biophoric molecules in place of one.

4. In such a system, so long as the medium and the physical environment remain the same, for so long will the constitution and properties of the biophoric molecules remain unaltered. There will, it is true, be a continual "come and go" of side-chains, so that at any particular moment the molecule as a whole will vary in weight, number of combined carbon and other atoms, etc., from its constitution the moment before; but the average composition will remain unchanged.

5. Alteration in environment, by inducing alteration in the nature and proportional amounts of the atoms and ions in the surrounding medium, must in such an unstable system bring about alteration in the composition of the molecule, provided always that there exists a positive affinity between the atoms or radicals of a new order entering the medium and the unsatisfied side-chains; the side-chain affinities must become satisfied in a different manner, and, as the form and properties of the individual are the expression of the composition of these biophoric molecules, the form and properties must inevitably undergo variation.

6. So long as a given alteration of medium persists, for so long will the form and properties of the individual present a particular alteration.

Variation must thus be regarded as primarily introduced by alteration in environment. This would seem to be the only factor causing variation in organisms in which sexual conjugation has not been developed; i. e., in asexual protozoa.

7. Studying such organisms, notably the bacteria, another property of the biophoric substance becomes obvious, the property which alone, with molecular change due to alteration of environment, has made possible the evolution of species. The longer, or the more intensely, a given alteration of environment acts upon bacteria, the longer it is before there is a return to the original characters when these bacteria are restored to their usual habitat. We can take a chromogenic microbe like the *microbaccillus prodigiosus*, and grow it for a short period at 30° C. or thereabouts, when it will produce colorless colonies; brought back to the room temperature and more normal environment, and the new colonies will rapidly resume the power of pigment formation. If the microbe be grown for weeks at a temperature just below the maximum, or be subjected for five minutes to a temperature which in ten minutes would surely kill every microbe in the test-tube, then it will be long weeks, and hundreds, not to

say thousands, of generations, before the power of pigment production is regained. Roux and Nocard cultivated for years, under the ordinary conditions of the laboratory, races of non-spore-bearing anthrax bacilli, in which the power to produce spores had been removed by temporary growth of the parent stock in solutions of carbolic and chromic acid just not powerful enough to destroy the organisms. Or otherwise altered environment does not of necessity merely alter the side-chains of the biophoric molecules during the period in which it acts upon the molecules; it may impress upon the general constitution of the molecules such an alteration of constitution that this is retained after reversion to the previous environment. That is to say, the affinities of the molecules may be more or less permanently altered. We can in this way not merely take away, but add properties to bacteria; we can, as Vincent has shown, render non-pathogenic bacteria actively pathogenic. It is only a matter of degree, not of kind, between the loss of these acquired pathogenic properties, when such bacteria are once more grown under ordinary laboratory conditions, and the loss of pathogenicity shown by definitely pathogenic species such as the bacillus typhosus when grown outside the body.

The work of the last few years in physiological chemistry indicates more and more clearly that when food-stuffs are assimilated, they are not taken up in an unaltered form and directly combined into the cytoplasm, but, on the contrary, undergo a disintegration into more elementary constituents, and these it is that, present within the cell and diffused in the spaces of the cell-substance, form the matter from which the biophoric molecules attract and combine the atoms and radicals which become built up into their substance.

Variation and the assumption of new properties indicate, therefore, that under the influence of altered environment the biophoric molecules gain the power of attracting new combinations of atoms and of forming side-chains of altered type. We are forced to realize that once the bioplasmic molecule has formed a new side-chain it tends to continue to form that particular form of side-chain by attracting particular orders of atoms and radicals from the surrounding medium, even when the old environment is again set up, and what is more, that sooner or later the new biophores built up from the side-chain materials come to differ in their constitution from the old.

The conception of properties of this nature on the part of a chemical substance may seem revolutionary. It appears to demand at first sight that a particular "ring" which at one time attracted as side-chains one particular group of atoms, obtains the habit of attracting another group, and this despite the fact that components of the former group are still in its immediate vicinity. But in imagining this we fall into the same error as did Weismann with his eternity of the germ-plasm. It is not the old "rings" that have taken on the new properties, but newly formed rings, developed primarily, it is true, according to our conception of growth, in connection with the old; but these nevertheless are separate combinations of radicals with slightly different arrangement of constituents and therefore slightly different properties and affinities.

8. The same is true regarding individual body-cells of the multicellular organism. Workers in bacteriology at the present day recognize

that the conception of central rings with side-chains capable of renewal and replacement by side-chains of another order, of satisfaction of the side-chains and casting loose of the same into the surrounding medium, is the only concept fitted to explain the phenomena of recovery from infection, and immunity. Under the action of bacterial toxins certain cells gain new or exalted properties. Certain side-chains, it is held, combine with and neutralize these toxins, and when satisfied these side-chains are cast loose and others are formed; nay more, are formed in excess and cast loose in an unsatisfied condition to form the antitoxic substances present in the blood-serum. In cases of long-continued immunity it is obvious that the bioplasm of the cells once incited to form side-chains having a specific reaction with specific toxins,—or with vegetable poisons such as abrin and ricin, is henceforth altered. The new biophoric molecules developed in the course of growth retain for a shorter or longer period the properties impressed on the earlier molecules, and this in the absence of the specific toxin or poison. Heredity, as distinct from variation, must be regarded as the expression of this tendency on the part of biophoric molecules to attract to themselves and build up into new biophoric molecules identical ions of atoms and radicals.

9. Before discussing sexual conjugation and its effects upon inheritance and variations, it is necessary to say a word regarding cell structure. The argument that in the nuclear matter is contained the heritable substance seems to us impregnable. We must regard the biophoric molecules as contained in the nucleus, and our conception of the cell and its peculiar structure in all higher forms of life must be that the division into nucleus and cytoplasm is an arrangement whereby the highly differentiated biophoric molecules, unable to act directly on the surrounding outer medium, become surrounded by an intermediate preparatory medium, the cytoplasm, the component molecules of which are not biophores. The nucleus alone cannot maintain life; neither can the cytoplasm alone exhibit growth. At most this latter can assimilate and form paraplasmic substances which in the absence of the nucleus do not become part and parcel of the bioplasm; the nucleus is essential for *growth*.¹

10. If we accept this view of the nature of the biophores it is not necessary to demand, as does Weismann, that there is conveyed to the offspring in the germ two forms of matter—that constituting the germ-plasm and that forming the somatic-plasm, the latter controlling the development of the individual tissues and cells of the organisms, the former alone able to react at the proper time and initiate the development of the offspring. Such a conception introduces unending confusion. Taking the simplest case, that of a multicellular organism developed asexually by parthenogenesis, our conception must be that as the ovum segments and the cells assume different relationships the one to the other, and to the surrounding medium, the influences acting on the various orders of cells vary, and with this variation the constitution of the biophores present and “growing” in the nuclei of the different cell-groups, undergoes a coincident alteration; so that, for example, the biophores in the eventual muscle-cell possesses a different constitution from those in a nerve-cell.

¹I have discussed more fully this dominance of the nucleus and its relation to the cytoplasm in an address at the Toronto meeting of the British Medical Association. *British Medical Journal*, 1906, II.

Whether such a specialized cell under any conditions multiplies and gives rise to the complete individual—as happens, to quote trite examples, in the case of certain cells of the hydra and with the cells of the begonia-leaf—depends upon the extent of the departure of the biophores from their primordial constitution in the germ-cell; or, perhaps more correctly, upon the tenacity with which they retain that original constitution. We may imagine that in such cases the central ring remains unaltered, the cell differentiation being the result purely of modification in the side-chains; the newly formed biophores, responsive to the change in environment, develop side-chains of the primordial type, and so are capable of developing the whole individual. The relationship of what are to be the germ-cells in a multicellular organism are such that in the process of their development the contained biophores depart least in constitution from the biophores of the ovum from which they have developed. Thus the properties of any individual cell are to be regarded as the outcome of (a) the constitution of the biophoric molecules passing into the cell at its formation as a separate unit; and (b) the alteration in those molecules and their derivatives induced by the forces acting upon the cell.

11. The biophores contained in the germ-cells of an individual are not those contained in the germ-cells of the parents; they are the outcome of the ovum by growth, and as in general they have been subjected to a like environment, so in general they have (with certain reservations to be discussed later) the same constitution. But just as with growth the biophores of the body-cells are capable of alteration in constitution, so in their growth the biophores of the germ-cells may be modified, and that by like causes; namely, by diffusible substances circulating in the nutritive fluids, as also by purely physical influences telling upon the organism as a whole.

The difficulty in determining that influences of this nature, telling upon the body generally, affect also the germ-cells, lies in this, that in man and mammals the growing embryo is nourished by the maternal tissues, and so where the mother is subjected to deleterious conditions it is difficult, not to say impossible, to distinguish surely between conditions due to pre-conceptional disturbance of the ovum and those due to placental absorptions after fertilization; and considering man more particularly, it is difficult to collect a sufficient number of cases in which the evidence is positive that the mother has been normal, the father alone the subject of one or other form of intoxication—alcoholic, tuberculous, etc.

It is, for example, a matter of common belief that paternal alcoholism is frequently associated with the development of offspring of a lower vitality, and more particularly exhibiting mental instability. I am inclined to hold that this belief is well founded. At the same time I must admit that sound statistical evidence in its favor is lamentably lacking. Similarly the influence of paternal tuberculosis alone, not as inducing active tuberculosis in the offspring, but in producing what may be termed *para-tuberculous* lesions, has not been adequately worked out. Too many other factors have to be taken into consideration: possible tuberculous diathesis already inherited by the parent, the environment of the young child, etc. Nevertheless we have a certain amount of evidence showing that this is actually the case—that paternal intoxication does influence the semen and leads to the production of vitiated progeny. More than one

recent observer has directed attention to the fact that in the case of monstrous births it is noticeable how frequently the history is obtainable that one or other parent had suffered from some acute infection shortly before conception. Mairé and Combemale¹ subjected male dogs to acute and chronic alcoholic intoxication and found that the young exhibited various arrests of development and were subject to epileptoid seizures. And as regards man, I have never seen any refutation of Constantine Paul's striking observations made in the "sixties" upon the effects of paternal lead-poisoning—cases in which in the course of his work the father was subjected to plumbism, the mother being unaffected. He obtained the history of 32 pregnancies of this order; of them 12 resulted in the death of the fœtus before term; 20 children were born alive but 8 of them died during the first year, 4 during the second, 5 during the third; only 2 were living, 1 of whom had reached the age of twenty. Children so born were found particularly liable to various nervous affections.

More recent work along the same lines is contained in the interesting studies by Lustig,² of Florence. Lustig was retesting the observations of Ehrlich and others upon the transmission of acquired immunity. To do away with the confusion introduced by intra-uterine existence he employed fowls, and rather than employ bacterial infections or toxins, he chose a vegetable poison abrin. By repeated inoculations of increasing amounts he gained an extremely high grade of immunity, so that for as much as two years the birds were unaffected by minimum fatal doses of the poison. While he was unable to demonstrate that the young had acquired any immunity—on the contrary they appeared to be more susceptible—he notes, without comment, one very remarkable fact, *viz.*, that mating together immunized animals even a year after the injections had ceased, the majority of the eggs did not come to maturity, but contained monsters, and even of the few chickens that were hatched several were very feeble and some showed distinct anomalies. The animals had apparently quite recovered from the injections, and the only explanation for this remarkable series of monsters must be that the germ-cells, both paternal and maternal, had been acted upon and permanently modified by the abrin. Unfortunately not realizing, apparently, the bearing of these results, Lustig does not seem to have studied the effects of mating an immunized domestic cock with a non-immunized hen. We have ourselves attempted work along these directions with rabbits, giving the bucks minute doses of lead-salts over long periods, and our results, so far as they go, would indicate that the germ-cells have been seriously affected. But unfortunately an epizootic of rabbit septicæmia so affected our experimental animals that we are unable to state more at the present moment than that our experiments certainly favored and did not contradict the view here indicated.

It may be objected that in all these cases we are dealing with degenerative and not progressive changes in the germ-cells. We would only reply, if our view regarding the constitution of the molecules of living matter at all approximates to the truth, then, if it can be shown that the biophores may be deleteriously affected by diffusible poisons, it is obvious that

¹ *Ctes. rend. Acad. d. Med., Paris*, March 15, 1888.

² Lustig: *Centralbl. f. allg. Pathologie*, 15, 1904, 210.

other combinations are possible, leading to what we would term favorable or progressive modifications in their side-chains.

If, therefore, we accept this variation of the biophores of the germ-cells by influences which affect the other tissues of the paternal organism, we gain a comprehension of why it is that not merely is the offspring not identical with either parent, but why it is not even the mean of the two parents.

12. We see also why it is that there is not an identical composition of the nuclear material from the two parents, which, uniting, originates the new individual; and that in the amphimixis or fusion of the dissimilar biophores we have another cause of individual variation.

What is the nature of this amphimixis? We cannot, with the data at our disposal, regard it as an immediate chemical combination of maternal and paternal biophores. In not a few forms in which the stages of segmentation of the ovum has been carefully followed it has been established that for a considerable period, at least, the paternal and maternal chromosomes, while lying side by side, remain nevertheless distinct; and upon chemical and physical grounds it is difficult to conceive a true conjunction or chemical combination between elaborate molecules of closely allied constitution.

This does not, however, mean that we are compelled to accept Weismann's theory that ids, or groups of biophores, derived from long generations back, each of which has preserved its individual characters, are contained in the germ-cell. No such deduction is necessary. The studies stimulated by Ehrlich's remarkable work indicate another and a more rational conception. We need but to refer what has been observed in connection with the phenomenon of cytotoxicity. To give an example: histologically, and in their functions, the red corpuscles of a horse and a rabbit or a guinea-pig are curiously similar. Yet clearly they are of different molecular constitution; the one cannot replace the other. Introduce the red corpuscles of the horse into the rabbit and they are destroyed; and, what is more, the injection of these corpuscles leads to such a reaction on the part of the rabbit's organism that its blood-serum for some considerable period possesses the power of breaking up the horse's red blood-corpuscles. That in nature the equine erythrocytes should gain admission into the blood of the rabbit is a sheer impossibility; nevertheless, the rabbit's tissues produce substances which destroy the foreign red corpuscles; they adapt themselves to dealing with a novel compound; and they do more—they continue to discharge into the blood-serum a substance which is capable of breaking up the red corpuscles so that the rabbit's serum now causes a rapid disintegration of the corpuscles of the horse, although the same serum may be without effect on the red corpuscles of other species. We explain this according to Ehrlich's theory by the development of side-chains on the parts of the cells (*i. e.*, of the cell molecules) of the one animal, which, uniting with the side-chains of the molecules of the foreign red corpuscles, set up such constitutional disturbance that the corpuscles become disintegrated. Here I shall not discuss the process at length. What I wish to call attention to is that now-a-days we accept this view that molecules of organic matter which are apparently closely allied in function and structure act the one upon the other not

directly, but through their side-chains, whether these chains remain attached to the central ring or whether these have become liberated and are free in the surrounding medium.

Let us apply this idea to the fertilized germ-cell. Our conception so far has been that the paternal and maternal biophores are of closely allied constitution. We may indeed regard the central rings in individuals of the same race as identical, the side-chains, or some of them only, as different. It is conceivable that when these allied biophores exist side by side within the germ-cell a process takes place similar to that above indicated. If we accept Ehrlich's theory in its broad outline we are justified in supposing that such allied though diverse biophores existing side by side are not inert; that as they grow—*i. e.*, as they assimilate other groups of atoms to form side-chains—through these side-chains they are capable of acting one on the other in the same way as molecules of different species—and even of different individuals of the same species—have been found to act one on the other, *i. e.*, through their side-chains. If, for example, the biophores of paternal origin form one particular order of side-chains, these, becoming liberated into the cytoplasm, may become attracted to and may satisfy the molecules of the maternal biophore; and just as certain cells in the rabbit in the presence of the horse's red blood-corpuscles gain the property to form new affinities when side-chains of the equine erythrocyte molecules are present in their neighborhood, so gradually with "growth" in association with the paternal biophores the maternal biophores may be modified to this extent that in them certain side-chains become replaced by side-chains of paternal type. This we regard as the true amphimixis—a gradual progressive interchange of properties and mutual rearrangement of constituent molecules tending in the main to the biophores of the two orders becoming identical, but varying in the results according to the nature and properties of particular side-chains, and this even though we accept Weismann's contention and regard the biophores and chromosomes of paternal and maternal origin respectively as continuing to occupy for some considerable period a definite position in the nucleus in regard one to the other.

Along these lines we can postulate cases in which the side-chains of a particular order from the one source completely replace those from the other—exclusive inheritance. We can further suppose cases in which they antagonize or neutralize each other, leading to the practical loss of the side-chains of one order, whereby the biophore assumes a simpler type of constitution; or, more exactly, the individual developed from the conjunction of the biophores of two orders is deficient in a particular property or group of associated properties. We can thus understand the phenomenon of reversion and of sports of defect. It is further possible to comprehend along these lines cases in which side-chains of a particular order augment each other—in which, that is, a biophore gains a combination of the side-chains of a particular order of both paternal and maternal origin. Or otherwise we can understand progressive inheritance and production of mutations and sports of excess.

In such a process of amphimixis as here indicated the tendency must clearly be that of replacement or augmentation of weaker chemical affinities by stronger ones; and so we should not expect to find that all the various

side-chains with their peculiar properties belonging to one set of biophores should replace those of the other set; or, in other words, that the biophores of the maternal type, for example, should wholly replace those of the paternal type. There would tend rather to be a certain amount of give and take and interchange depending on the affinities of the particular biophores. Further, it is essential to regard the side-chain molecules as attracted in series to form chains. And, also, judging from what we know regarding immunity, we must infer the existence of the law that the properties of the oldest acquirement are most tenaciously retained, and those of most recent acquirement most easily lost. Or, otherwise, granting that a biophore or biophoric molecule acquires new side-chains in this interaction with biophores of different origin, if that biophore and its products be removed from the influence of this interaction it may, with relative ease, lose the power of forming these newer combinations, and in a new environment revert to the earlier affinities and properties.

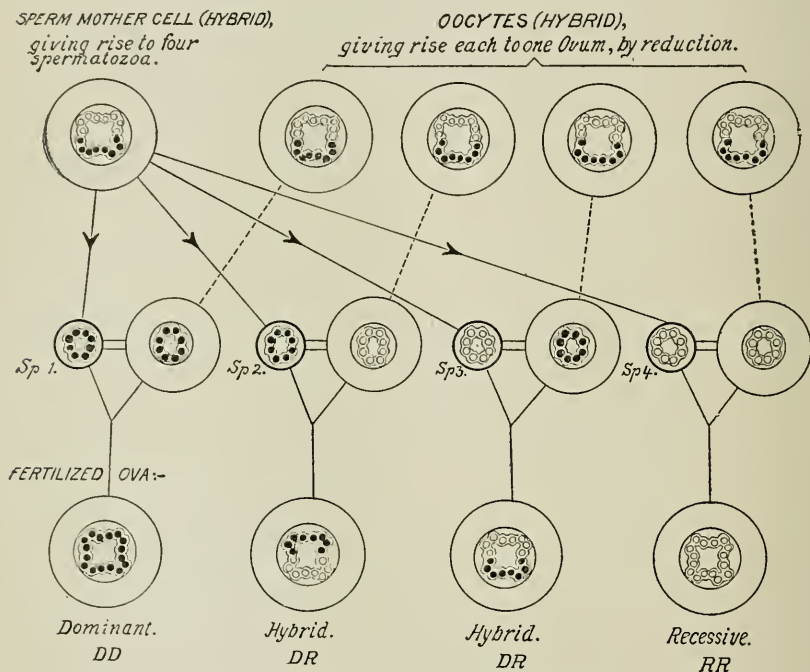
But to enter at length into these different possibilities regarding the interaction of maternal and paternal biophores in the germ-cells is beyond the scope of this article. It may indeed be urged that we have already entered into this matter at too great a length, even though we have sought to compress our presentation of the theory into the smallest possible space compatible with clearness. But having mentioned and accepted Mendel's law for cases of exclusive inheritance, it is necessary that we should indicate how the theory applies to this particular order of phenomena.

Suppose we take four marbles, two black and two white, and shaking them together let them fall out of the box two and two, and in doing this test how often we obtain in successive casts, (a) a pair of blacks; (b) a pair of whites; and, (c) a combination of one black with one white. A little consideration will show that the chances are equal that the first marble to emerge will be either black or white, and that they are equal whether the first combination to be cast will be a pair of the one color or a combination of the two. If the first pair to emerge be a black pair the next must be a white pair; if the first two out of the four marbles be a white and a black, the next two must also be white and black. The same will be true whether we deal with only two pairs or 200 pairs. Or, otherwise, for every B B and W W combination recorded once the B W combination will be recorded twice, and the sum of repeated casts will be some multiple of the formula $BB + 2 BW + WW$.

It would seem obvious that to explain Mendel's law we must accept the view that in the germ-cells the paternal and maternal chromosomes (with their contained biophoric molecules) do not fuse, but remain independent if associated series, undergoing coequal growth and multiplication as the germ-cells proliferate (as indeed would seem to be indicated by the studies of Conklin and Häcker). What is the simplest—we do not say that it is the correct—method of grasping what happens is to suppose that the nucleus of the sperm mother cell at one stage, of what Moore terms the maiotic process, presents a complete separation of the chromatin of paternal and maternal origin respectively, so that of the four spermatozoa which eventually result, two carry on the biophores of paternal origin, two those of maternal. And similarly that in the development of the ovum, with the discharge of the first polar body all of one group of biophores either paternal or maternal become removed, and

with the discharge of the second polar body there is reduction with loss of one-half of the chromatin, whereby the ovum comes to contain an amount of chromatin—or number of biophores—of either paternal or maternal descent, equivalent to the amount of chromatin and number of biophores in the ripe spermatozoön. If now these ova and spermatozoa fuse, as indicated by the diagram, the proportion of progeny afforded by the hybrids will be in the proportion demanded by Mendel's law. In the diagram the black dots indicate dominant, white circles recessive, biophores, as well as paternal and maternal origin.

FIG. 3.



To afford Mendel's formula for cases in which there is more than one pair of mutually exclusive properties it is necessary to invoke in addition the principle already dwelt upon; *i. e.*, that of interchange of side-chains between the biophores of the two series. We must suppose that while the series of developing biophores of maternal or paternal origin remain distinct, those of the one set have the greater affinity for particular orders of side-chain radicals. We must conceive them as attracting those orders and leaving the others to be taken up by the other set. By this means, although the biophores of the one set would still remain in series, the side-chains would become crossed, and by successive acts of fertilization, there would be developed the series of forms represented by Mendel's formula.

Complicated as the theory must seem when first read, the more it is studied the more fully we believe it will be found to fit in and accord with the facts at present known and established with regard to heredity. We

owe it perhaps to ourselves to explain that it has not blossomed suddenly, but is the outcome of more than fourteen years of study, the basal conception—that primarily variation is due to altered environment—having been borne in upon us by an investigation into the variability of bacteria, in 1891.¹ Its development, we may add, has essentially been brought about by a consideration of the problems of the inheritance of morbid conditions. We may add that it gains strong support from recent botanical studies which show that by the action of external agents upon the ovules of seed plants, certain parental qualities may be suppressed and new qualities gained, and this it would seem not temporarily, so that actual departures from the course of the hereditary strain may be induced.²

To sum up briefly our views with regard to the inheritance of disease, they may be expressed as follows:

1. There cannot be homologous inheritance of gross structural disturbances.
2. There is no true inheritance of infectious disorders.
3. The only possible inheritance of conditions acquired by the parents is that of conditions which act upon and affect the bodily tissues of the parent and affect also the germ-cells.

These conditions may be of two orders:

(a) **Extrinsic and Direct.**—Chemical and physical conditions introduced from or acting from without may simultaneously bring about modifications in the constitution both of the somatic- and the germ-cells. As the germ-cells are part and parcel of the parent at a period when such a modification could or does occur, it is futile to urge that such modifications are not strictly instances of transmission of parental acquirements. If this be accepted we must admit that parental intoxications, whether from absorbed chemical substances or resulting from the growth of pathogenic organisms, may influence the organism, and that, in all probability the different toxins or poisons, acting differently upon the molecules of the germ-cells, may lead to the offspring becoming modified in its development in one or other particular direction.

(b) **Intrinsic and Indirect.**—It is conceivable that specific influences acting upon one or other organ of the parent, or again the destruction or arrest of action of an organ or part, may so disturb general metabolism that the absence of normal metabolites or presence of abnormal metabolites in the circulating blood may influence the nutrition of the germ-cells, bringing about alterations in the constitution of the germinal biophores and resulting alteration in the constitution of the offspring.

Metabolic disturbances in the parent—gout and the rheumatoid states, for example; defect or excess of internal secretions—may tell upon the germ-cells. It is conceivable that the organism as a whole which originates from the modified or weakened germ-cells may exhibit a special susceptibility toward the effects of that particular order of compounds which primarily caused alterations in the constitution of the molecules

¹On the Variability of Bacteria and the Development of Races, *Manchester Medical Chronicle*, September, 1892. Other articles upon 'Growth' (Jacobi, *Festschrift*, 1900, and on Inheritance, *New York Medical Journal*, 1901, and *Buck's Reference Hand-book, Heredity and Disease*, 2d edition), show the development of the views here brought forward.

²See D. T. Macdougall: *Popular Science Monthly*, September, 1906.

of the germ-cell. Along these lines we best comprehend the development and inheritance of *diatheses*.

While admitting these possibilities, two counteracting influences have nevertheless to be kept in mind: (a) The fact that the individual is the product of the interaction of the germinal matter derived from two sources whereby the constitution of the germinal matter from the one parent may be neutralized in its effects to a greater or less extent by the constitution of the germ-plasm from the other parent (the many different ways in which this interaction may show itself need not here be recalled; they have been discussed and classified in the preceding pages); and (b) the action of the law already noted that properties of recent acquirement are those which are most easily lost; so that biophores modified by subjection to temporary influences may upon reversion to a more normal environment give rise to new biophores approximating to or gaining the original constitution.

There may further be a true inheritance of morbid conditions due not to the transmission of a property or defect through the germ-cells of either parent (and observable, if not in the parent, at least in the parental stock), but to the interaction of the two germ-plasms in fertilization; or, more exactly, due to the modification in the biophoric molecules by the interaction of their side-chains.

PART II.

DISEASES CAUSED BY PHYSICAL AGENTS.

CHAPTER II.

LIGHT. X-RAYS. ELECTRICITY.

By ALFRED GORDON, M.D

PHYSIOLOGICAL EFFECTS OF LIGHT.

THE modern conception of organic and inorganic life embraces various conditions. They are not all equally necessary for living organisms: while some are absolutely indispensable, others play only a secondary role. Light belongs to the category of objects without which both plant and animal life are impossible. Light makes available chemical energy in the plant-cell, and out of this energy are derived all the activities of the plant in a complex series. It is an established fact that out of carbonic acid and water which leave the animal body, the plant-cell, under the influence of light-rays, creates an endless chemical energy. The favorable effect of light and chemical rays of the sun upon animal life had been known from most ancient times. The sun was considered as the source of life, and therefore worshipped (Helios, Apollo). The ancient Egyptians and Assyrians devised various appliances which they placed on the roofs, and there they exposed their bodies to the rays of the sun, as they believed in the invigorating influence and great curative power of light. Hippocrates, the father of medicine, was convinced of the curative properties of sunlight; also of its influence on the skin, and of its value in the sick-room. The Italian proverb, "All diseases come in the dark and get cured in the sun," is very significant. It is sufficient to recall Moleschott's experiments on frogs: placed in the same conditions of temperature, they exhaled more CO_2 in the light than in obscurity. Experimental physiology and clinical observation show that the respiratory

chemistry, formation of hæmoglobin in the blood, growth of the organism, and pigmentation of the skin, are directly dependent in a large measure upon light. Finally, functions of various glands and metabolism in general are undoubtedly in some relationship to light. Forbes Winslow has shown the effect of light on the growth of man. Growth of children during the months poor in sunlight is slow; this is particularly noticeable in children of the poor who live in basements. Cretinism is known to exist in dark mountainous valleys where the sunlight penetrates exceptionally. That the very existence of certain organs depends upon light-rays can be seen from the well-known observation that the eyes of animals kept in darkness generally become rudimentary.

Besides the direct physiological effect on the functions of the organism, light has also a beneficial effect upon the nervous system and psychic sphere. Disposition, humor, general sensations, will certainly be more agreeable in a clear, sunny day than in cloudy and gloomy weather.

Nature has provided us with light also as a means of defense against pathogenic microbes. That the tubercle bacillus may be destroyed by light has been proved by Koch and others. The favorable results obtained in the treatment of pathological conditions of the skin according to Finsen's method are perhaps due to its effect upon microorganisms. The action of light as described above is, according to the state of our present knowledge, due to the permeability of the skin and other tissues. Bouchard has shown that it is principally the ultra-violet rays that penetrate the tissues; the reflex stimulation is then transmitted through the skin and from the latter to the central nervous system, which in its turn influences various organs. The result is that life-processes and metabolism are increased.

PATHOLOGICAL EFFECT OF LIGHT.

If moderate light, as we have seen, has a favorable influence on the entire organism, intense light, on the contrary, acts unfavorably. The degree of injury naturally depends upon the intensity of and length of exposure to sunlight. Locally one may observe sunburn, which in mild cases is manifested in a simple erythema, and in severe cases in an inflammation with swelling and even destruction of skin. Freund, among others, has shown that in such cases a large number of ultra-violet rays traverse the epidermis and reach the deep layers of the skin, in which they affect the cellular elements. When cedema and exudation, with subsequent destruction, take place, a general reaction, with elevation of temperature, will follow. In extremely severe cases, when destruction is extensive, internal complications may ensue. In ordinary cases of sunburn, pigmentation may occur; the latter is, according to Finsen, a natural protection against further effect of light-rays.

Exposure to sun-rays may be an exciting cause for various affections of the skin in predisposed individuals. Lentigo, for example, is the well-known freckles, which appear usually on the face, neck, and hands; they disappear almost entirely during winter and reappear in summer. Chloasma, xeroderma pigmentosum, hydroa, and even pellagra, are all cutaneous affections in which sunlight plays a certain role as a causative agent.

The skin is not the only organ which may suffer from the immediate effect of intense sunlight. The eye may become affected. Ophthalmia and conjunctivitis are not infrequent occurrences in the polar regions and in the mountains. A few cases were reported in which cataract was apparently produced in workmen whose eyes were exposed to prolonged action of intense light.¹

All these changes, and particularly those of the skin, are the result of the effect of light-rays in a comparatively mild degree. The produced lesions are usually limited to the tissue exposed to the light. When the effect of intense sunlight is manifested in general disturbances, the condition may become alarming, as it may terminate by death. We speak then of sunstroke.

The term "sunstroke" has been considerably abused. Heat-exhaustion, heatstroke, sunstroke, insolation, coup de soleil, heat-asphyxia, and thermic-fever, have been described as one condition. Manson, in his book on tropical diseases, brings some order in the terminology, and his classification is, in my judgment, the most satisfactory. He considers separately a condition produced by the elevated temperature, to which he gives the name "heat-exhaustion;" another condition produced apparently and only by the direct rays of the sun, to which he gives the name "sun-traumatism;" and, finally, a third morbid state, to which Sambon gave the name "siriasis." The latter is in all probability due to a microorganism which develops only in a high atmospheric temperature.

1. Heat-exhaustion.—This condition is characterized by a sudden tendency to syncope in an atmosphere with a high temperature. It can be brought on indoors or outdoors. The main etiological factor is heat from any source. It is observed in industrial plants where work is carried on at temperatures above 120°F. Individuals suffering from various diseases, those whose physiological activities are lowered by alcoholic or other excesses, or by exhaustion, present very little resistance to the effect of heat. With the syncope occurring from heat-exhaustion are also observed the following symptoms: shallow respiration, small and soft pulse, dilated pupils, cold skin, and subnormal temperature. Recovery usually follows, but very occasionally death may ensue.

Heat-exhaustion brought on by exposure to the sun is called sunstroke, insolation, or coup de soleil. This condition is of great interest, especially to military surgeons; insolation in the army during summer months is of frequent occurrence. In warm climates those who are compelled to work outside of dwellings are apt to be stricken. Those who use alcohol are particularly predisposed to the effect of intense heat, and they constitute the majority of the victims of sunstroke. Some individuals are peculiarly predisposed to repeated attacks. Four cases came under the writer's personal observation, when the patients, free from alcoholism, had three attacks during three successive summers. Among other predisposing causes we may mention excesses of all kinds, constitutional diseases, or low vitality following protracted diseases. Finally, any cause which prevents the evaporation of the perspiration, as, for example, clothing fit only for cold weather and worn on hot days, predisposes to sunstroke. It is interesting to note that the black race is remarkably resistant to the

¹Wm. Robinson, *British Medical Journal*, January 24, 1903

effect of intense sunlight. Cases of insolation in children are also rare. As we see, the subject is of sufficient importance to warrant a more detailed description.

Sunstroke (Insolation)—Symptoms.—In the majority of cases a sunstroke is preceded by a few premonitory symptoms before complete prostration sets in. They are headache, dizziness with generalized tingling sensations, and nausea. Pain in the epigastrium, vomiting, and excessive thirst soon make their appearance. Consciousness is retained in mild cases. The patient enters into a state of exhaustion, which may go to complete prostration and end in death quite rapidly. If he survives, a slight fever may be present, which gradually goes down to normal. The above-mentioned symptoms then gradually subside and complete recovery takes place. Before recovery occurs the patient will complain for a long time of headache; this is practically the only symptom which persists after others have disappeared. In severe cases of insolation there is always a loss of consciousness, which may be followed by death; the latter is rather exceptional. In a great majority of cases the patient regains consciousness; but there is extreme pallor, rapid respiration, rapid pulse, which is soon succeeded by a slow pulse; temperature is raised to 104° or 105° and in very severe cases to 108° . In some cases the temperature reached 112° – 113° , which, according to certain observers, is not uncommon in severe forms of insolation. The skin is usually dry or covered with a clammy perspiration. Convulsions, epileptiform in character, may occur, while general muscular twitching is exceedingly common. Delirium is not an infrequent occurrence. The entire body is either in a state of rigidity or absolute flaccidity. Ecchymosis, or a petechial rash, was observed in a certain number of cases.

The severity of certain cases is not dependent upon the degree of the temperature or upon the state of the pulse, and it is therefore difficult to foretell exactly the issue of a given severe case. Despite the unusually pronounced symptoms, recovery may follow, although not without a persistent headache and various paræsthetic disturbances, as tingling, numbness, pins and needles, etc., or some physical and intellectual weakness. Generally speaking, patients who remain unconscious for twenty-four or forty-eight hours usually die.

Sunstroke is one of the causes of chronic meningitis, and the cephalæa which so frequently follows recovery from insolation finds its explanation in the meningeal involvement. Far more important and frequent sequelæ of sunstroke consist of distinct mental disturbances, as impairment of memory or of sustained attention. Some writers pretend that delusional insanity, paresis and mania may be caused by insolation. The writer's view is that if insolation is sometimes followed by these mental derangements, it is only as an exciting cause similar to trauma; patients of this character undoubtedly were predisposed to insanity or were already insane, and exposure to intense sun radiation only intensified the condition. Among other possible consequences of sunstroke we may mention polyuria and glycosuria.

Pathology and Pathogenesis.—The gross pathological changes found in cases of sunstroke may be expressed in one phrase: general congestion of the organs. The lungs, liver, spleen, and particularly the meninges of the brain and cord, are in a state of congestion. The blood is very fluid.

The microscopical studies of various tissues and organs have shown that the cells of the liver and kidneys and of the nervous system all undergo parenchymatous degeneration. The nervous system suffers particularly, and there the changes are similar to those found in cases of intoxication with poisons, as lead or alcohol; namely, marked chromatolysis of the cells. The condition of the blood deserves special attention. Leukocytosis and in some cases destruction of erythrocytes with diminution of the alkalinity of the blood are the changes which occur.

As to the pathogenesis of the disease, there is a great divergence in the theories which have been advanced to explain the symptoms and death in insolation. Vallin at first believed that death is due to heat coagulation of the cardiac muscle. Hirsh believes that the cause of death lies in alteration of the blood—diminution of oxygen and retention of a toxic principle. Vincent¹ arrived at the conclusion that there is a poisoning of the organism by toxic products accumulated in the blood. According to Laveran and Régnard,² who made an extensive experimental study of the question, death in insolation is due to a direct effect of sun-rays, principally upon the nervous system; this effect is first excitant and then paralyzing. The investigations of more recent writers tend to the conception of a paralyzing action on the nervous system of some toxic elements, with the probable result of metabolic changes in the neurons; and according to the degree of auto-intoxication the effect of the sunstroke will be either an attack of ordinary heat-prostration or syncope with unconsciousness or death.

Diagnosis.—It is only in exceptional cases that the diagnosis will be difficult. Usually the history of exposure, with the high temperature and the condition of the skin, render the diagnosis easy. In some cases, however, especially when there is a history of alcoholism or cardiac lesion, the diagnosis will be difficult; apoplexy should then be thought of. In the latter case the temperature is usually normal, the breathing is stertorous, the pulse is slow; but the most important symptom is the local paralysis, hemiplegia, or monoplegia. In malarial districts, a pernicious malarial paroxysm may give difficulty but a blood examination will make the diagnosis clear.

Prognosis.—The outlook in cases of sunstroke will naturally depend upon the degree of prostration, and, according to some authors, upon the temperature. The latter condition is not absolute, as the writer has observed a patient with 110° who recovered. However, on general principles a very high temperature renders the prognosis unfavorable. The previous general health, and especially whether the patient uses or does not use alcohol, is of utmost importance in forecasting the outcome of his sunstroke. The promptness of rendered assistance and the character of the treatment are also factors which play an important role in determining the prognosis of a given case. In mild cases of heat-prostration the prognosis is favorable. As to the complications following sunstroke, they are all as a rule temporary, except the grave forms of insanities. As in the latter, sunstroke similar to trauma plays only the role of exciting factor, the prognosis will be not dependent upon the insolation. In some cases the sequelæ of sunstroke are very rebellious to treatment, and may

¹ *Rech. exper. sur l'hyperthermie*, 1887.

² *Bull. d. l'Acad. de Méd.*, 1894.

persist for a long time. Finally, as we said above, some patients become predisposed to repeated attacks after they have once had a sunstroke.

2. Sun-traumatism.—Under this name Manson describes a morbid state characterized as a rule by sudden death occurring without warning after exposure to the sun. Paralysis of the heart or respiration seems to be the immediate cause of death. In a certain group death may not ensue, but the patient exhibits symptoms of meningitis; namely, fever, headache, dry skin, rapid pulse, photophobia, and vomiting. The condition is not invariably fatal. If recovery follows, there are always sequelæ more or less persistent in character, as tremor, amaurosis, amnesia, deafness, epilepsy, and paralysis or paresis of the extremities.

As to the pathogenesis of sun-traumatism, it is highly probable that caloric is not at fault, as similar effects have not been observed from exposure to heat from other sources—as a furnace, for example. Manson is therefore justified in presuming that there is a special element in the solar spectrum capable of injuriously affecting the tissues, particularly if they have not become gradually habituated to sun exposure. To corroborate this view Manson calls attention to the phenomena of sun-erythema, of skin pigmentation known as sun-burn, and possibly of leukoderma; also to the sensation of distress brought on by exposure to a hot sun, which is quite different from that produced by the heat of a fire.

3. Siriasis.—This is a specific disease developing in high atmospheric temperature, and, similarly to yellow fever or dengue, is not caused by the elevated temperature, but probably by some microörganism which demands for its development a high atmospheric temperature and certain local conditions. It is known on the east coast of the United States and the South Atlantic coast; in Africa, Asia, and Australia. The mortality from this disease is very great. According to Manson (*Tropical Diseases*) the case mortality among English troops is about one in four. The symptoms observed are almost identical with those of sunstroke, and are characterized mainly by hyperpyrexia, coma, and extreme pulmonary congestion. If a post-mortem examination is made shortly after death and before decomposition changes have set in, the heart is found to be remarkably rigid. Rigor mortis is an early appearance. The blood is remarkably fluid and yields an acid reaction. Venous engorgement of the viscera is a notable feature.

Treatment of Heat-exhaustion, Sun-traumatism, and Siriasis.—The first indication in cases of heat-prostration, be it mild or severe, is rest. The patient must be undressed and put to bed; if stricken on the street, his clothing must be loosened and he should be laid on his back in a cool, airy, and shaded place. The next indication is application of cold to the head, and some stimulant (brandy or others) administered. In mild cases this treatment will be sufficient. In more severe cases, in addition to these means, some drug may be given to alleviate the headache and reduce the high temperature. The coal-tar products, salicylates, etc., will answer both indications, but should always be used with caution. When, on the contrary, the prostration is very pronounced and the temperature is below normal, heat instead of cold will have to be applied,—in conjunction with some internal stimulant, if there is no coma; if coma, stimulants must be given hypodermically. Strychnia, camphor, and nitroglycerine, are the usual drugs for the latter purpose. Convulsions

can be controlled by placing the patient in a lukewarm bath and by administration of morphine aided by atropine. Restlessness and insomnia are best treated by the bromides. High temperature can be controlled particularly by cold spongings frequently repeated, or by cold baths, the temperature of which is gradually reduced while the patient is in the tub. The patient should be vigorously rubbed. The same procedure can be employed in cases of unconsciousness. These hydrotherapeutic measures can be modified according to the conditions in each individual case. If baths are not convenient, cold packs may take their place. Sometimes a shower-bath, or a douche over the spine, of short duration and followed by a dry rubbing, reduces the temperature admirably besides having a stimulating effect. It should be borne in mind that while the patient is treated with cold water, stimulation with the above-mentioned means be kept up. Among the stimulants the writer lays special emphasis on saline infusions, which in many cases prove to be an excellent adjuvant. If the patient is a full-blooded individual, venesection followed by saline infusions will be of better service than infusion alone. When death is imminent, repeated stimulation with the usual remedies and artificial respiration must be used.

After the pronounced symptoms have disappeared, the treatment will be symptomatic. Headache, insomnia, nervousness, paræsthetic disturbances, should be treated accordingly.

When the hyperpyrexia is great, as, for example, in siriasis or in extreme cases of insolation, all the efforts must be directed toward reducing the temperature by rapidly acting measures. Chandler's¹ directions are of great value in such cases. He advises to put the patient, undressed, on a stretcher the head of which is raised slightly so as to facilitate the escape of involuntary evacuations and to provide for drainage. A thermometer is kept in the rectum. The body is covered with a sheet upon which is laid numerous small pieces of ice, larger pieces being closely packed about the head. Ice-water is then allowed to drip for thirty or forty minutes on the patient, from drippers hung at an elevation of from five to ten feet. A fine stream of iced water poured on the forehead from an elevation will act as a stimulant; this powerful measure must not be kept up for longer than one or two minutes. A hypodermic injection of forty minims of tincture digitalis is given as soon as possible, its administration being preceded in the case of plethoric patients by a small bleeding. As soon as the rectal temperature has sunk to 104° the application of cold should be at once discontinued. On discontinuing the iced sheet, the patient should be wrapped in a blanket and hot bottles applied to limbs and trunk. In this stage strychnia as a stimulant should be avoided. In case of failure of respiration, artificial respiration should be resorted to; Chandler urges to keep it up for half an hour. There is a very important warning given by Manson. Antipyretics (antifebrine, antipyrine, etc.) should by all means be avoided, as they are dangerous in view of their depressing action on the heart.

If the treatment of sunstroke as outlined here will save some patients, the prophylactic measures are of greater importance. The above-mentioned investigations of Laveran and Régnard, also those of Hiller, show

¹ *Medical Record*, New York, 1897.

that prolonged physical exercises facilitate the onset of sunstroke. It is therefore advisable in hot days to avoid as much as possible all causes of fatigue. As alcoholic intoxication predisposes to sunstroke, beverages containing alcohol must be avoided. Excesses in the use of animal foods and others, violent exercises, want of sleep, constipation, etc., should be avoided. Individuals suffering from malarial or other fevers, or from chronic liver or kidney diseases, run great risk in exposing themselves carelessly to the sun. Unnecessary exposure to the sun in summer is contraindicated. A hat should be always worn in hot days in order to avoid a direct effect of the sun on the head. We should not expose ourselves to sun-rays more than an hour, as very long exposure brings on high excitement or complete relaxation. Much sweating weakens and provokes chills; a skin which perspires is a better conductor for chemical rays than a dry skin.

Before the discovery by Röntgen of rays to which the scientific world attached his name, our knowledge of sources of light was limited with the spectrum, and all we know about physiological effect of the latter is that only the blue, violet and ultraviolet have a vital function in animal life.

THE X-RAYS.

The discovery of x -rays revolutionized our knowledge of the composition of light. Since 1896, physicists have applied themselves arduously to the further study of various sources of light, and we are now in possession of Becquerel's rays, of radium, of polonium, actinium, Blondlot's and Charpentier's N and N' rays respectively. Some of these rays have proven to be of certain therapeutic value; others are only in an experimental stage. Röntgen's rays have almost accomplished their history. Their application in medicine is of inestimable use, both for diagnostic and therapeutic purposes.

The therapeutic effects of x -rays became particularly known since Freund applied them with success for the first time on a *nævus*, and Kummel with Gocht on *lupus*. Since then various dermatoses were treated, namely, *favus*, *sycosis*, *hypertrichosis*, *acne*, *eczema*, *psoriasis*, *prurigo*, *alopecia*, and *ulcerations*. Soon neoplasms, both malignant and benign, were submitted to the action of x -rays. The results were so encouraging in a great many instances that their beneficial effects became universally recognized. At the present day many operable and inoperable cases of tumors, both external and internal, receive the x -ray treatment, before or after surgical interference. The beneficial results obtained so far led a number of men to extend the application of the new treatment, so that there are on record cases of *neuroses*, and even organic diseases, some symptoms of which—pain, for example—derived benefit from x -ray treatment. Some observers treated with favorable results cases of progressive pernicious *anæmia*, *leukæmia*, *Hodgkin's disease*, and *exophthalmic disease*.

Inasmuch as good results are obtained from x -ray treatment, we meet now and then with accidents, in which the deleterious effect of x -rays may go so far as to produce permanent lesions, with complete destruction of tissues.

PATHOLOGICAL EFFECT OF X-RAYS.

The disturbances produced by x -rays are (1) local and (2) general.

1. Local—Dermatitis.—The first case of x -ray burn we find mentioned by O. Leppia;¹ and the first case of alopecia caused by x -rays was reported by Daniel.² Since then a large number of observations were made and recorded, all showing that while we have in the x -rays a powerful physical remedy, nevertheless it must be handled with greatest caution and with full knowledge of its physical properties.

It is generally accepted that the specific effect of x -rays consists of eventual destruction of tissue, (analogous to the ultra-violet rays of the spectrum when they are in superabundance). Ulcerations, necrosis, and sloughing of skin, are frequent occurrences in exposures to x -rays. The consensus of opinion concerning x -ray burns is that the latter undergo three stages, namely: (1) Hyperæmia, leading to exfoliation in scales, degenerative changes with subsequent atrophy in the tissues depending upon the skin, as hair, nails, glands, etc.; (2) vesiculation; and (3) escharotic destruction; the intima of the blood-vessels becomes thickened and the whole process presents a chronic inflammation with all its usual consequences. Freund described increase of pigment in the cells of the Malpighian layer of the epidermis. The histological changes affect chiefly or exclusively the cellular elements of the skin, which undergo a slow degeneration with destruction, while the connective, the elastic, the muscular, and the cartilagenous tissues are not at all or only in a slight degree altered; or, if they do suffer, it is only secondarily to the inflammatory reactions. As to cells themselves, the epithelial cells are affected first; in a slighter degree are affected the cells of glandular organs and of vessels. The nucleus suffers conjointly with the cell-body. If the x -rays are intense, the leukocytes of the dilated vessels penetrate into the degenerated cells, and as phagocytes bring on their complete destruction and resorption. The cicatrization is of especial character; it is irregular, without a tendency to retraction, and perfectly white.

The x -ray burn has its *symptomatology*. At first there is a tingling sensation, which is followed by redness and swelling similar to the effect of solar rays. Later vesicles appear, which finally break down, leaving a raw surface. In severe cases ulcerations will follow the vesiculation. As the process is inflammatory, a few general symptoms may be present; namely, chills, fever, pain, general malaise, etc. The characteristic feature of the lesions is their late appearance. The initial paræsthetic disturbances may exist from a few days to two or three weeks before the erythema with the subsequent symptoms will be manifested. Bar-Bouille reports a case of severe burn with ulceration appearing two months after exposure. This is perhaps due to the cumulative property of x -rays, a fact which is accepted by all workers in that line. The healing process is also slow.

Other Local Effects of X-rays—(a) Atrophy of the Skin.—H. E. Schmidt, Kienbock, Gocht, Albers-Schönberg, Hahn, and Scholz, reported cases of marked atrophy of the skin, with dystrophy or shedding

¹ *Deut. Med. Wochenschr.*, 1896, No. 28.

² *Medical Record*, New York, April 25, 1896.

of the nails, following x -ray exposure. They were probably due to angio-neurotic and trophoneurotic processes.

(b) **Alopecia**.—In connection with this disturbance it is well to mention Gerwood's observation: in one case of his, curly hair grew in place of smooth; and in another black hair took the place of white.

(c) **Scleroderma-like** changes have been reported by Hallopeau, Fournier, Barthélemy, Gadaud.

(d) **Gangrene** has been observed by some writers.

(e) **Cancer** was first reported by Allen and then by a few others.

(f) **Swelling of muscles** was observed by some French workers in x -rays.

(g) **Lesions of the eye** leading almost to complete blindness. W. Rollins¹ made animals blind by x -rays. Cases of optic neuritis, ulceration of the cornea, conjunctivitis, myopia, amblyopia, and amaurosis, are on record. Periostitis and otitis have been observed by a few writers.

2. General Symptoms.—Oudin, Barthélemy, and Darier, who made extensive experimental studies and clinical observations, observed gastrointestinal disorders from x -ray exposure, as, for example, symptoms of gastritis from exposure of the abdomen. Vertigo, nausea, headache, insomnia, rise of temperature, general nervousness, tremor, palpitation of the heart with oppression, and in some rare cases slight cerebral disturbances constituting the symptom-group of meningitis, were observed following x -ray treatment. An established dermatitis may be accompanied in exceptional cases by a general illness. Holzknecht observed an intermittent vesperal fever (103° F. and above), chills, and concentrated urine. Fever usually lasts only a few days and ends with the beginning of a new skin. In four cases he observed skin lesions with a high temperature, which were taken for the eruption of scarlet fever. It is noteworthy to mention occasional occurrence of general toxæmia following x -ray treatment of cancer and sarcoma; this is probably due to auto-intoxication produced by the cancerous and sarcomatous material. In exceptional cases, paralysis (mono- and paraplegia) and convulsions were observed. Finally, death followed in a few cases of x -ray exposure. In these cases this was secondary to a general septic condition brought on by deep ulcerations with suppuration, but not by direct action of the rays;² at least the histories of the cases are not convincing.

Effect of X-rays on Internal Organs, with Special Reference to the Generative Organs.—The effect of x -rays on internal organs has been the subject of investigation since 1903. Senn, B. Ahrens, Krone, Fried, and Hahn, were the first workers in this field. Leukæmia and diseases of the spleen were reported as being very favorably influenced by x -ray exposures. Heineke examined microscopically spleens of mice and guinea-pigs which were submitted to x -rays for seven to fourteen days. He found excessive increase of pigment and disappearance of follicles. The changes in the latter occurred long before other degenerative processes made their appearances in the spleen and the epidermis; the so-called latent period and cumulative action which are observed in epidermis are totally absent in adenoid tissue. This was observed not only in the spleen but also in the lymphoid glands. The investigations of Boermann and

¹ *Boston Medical and Surgical Journal*, 1903.

² See H. E. Resmer's case, in *New York State Medical Journal*, 1903, p. 296.

Linser have shown that x -rays attack first the bloodvessels and especially their intima; all other phenomena are secondary to this effect. Milchner and Mosse described changes in the bone-marrow; Birch-Hirschfeld observed optic atrophy after exposure to x -rays. Symptoms of paralysis in small animals have also been noticed by some investigators, showing involvement of the nervous system. Whether in the latter case there were real pathological changes or only a dynamic disturbance, it is difficult as yet to tell. At all events the effect of x -rays on internal organs became an acquisition of science, and facts began to accumulate. Among these the most interesting and important are those concerning the effect of Röntgen's rays on the generative organs.

Albers-Schönberg¹ was the first to observe that x -rays produced sterility in rabbits and guinea-pigs without any change in the sexual potency. Death of spermatozoa was the immediate cause. AzoöspERMIA and atrophy of the testicles followed. The experiments consisted of daily exposures for 15 to 30 minutes, and about 195 to 377 minutes were necessary to produce the desired results. According to Friebe², the reason of the azoöspERMIA lies in the disappearance of the epithelium of the seminal canals, which leads to atrophy of the testicles. Seldin verified and corroborated in all its details the discovery of Albers-Schönberg and Friebe's explanation of the azoöspERMIA. A year later Buschke presented at the International Congress of Dermatology macroscopical and microscopical specimens of testicles atrophied from x -ray exposure. Philipp reports similar observations made in man. His first patient was a man of twenty-five with personal and family histories of advanced tuberculosis. In order to avoid an increase in his family, he accepted willingly the proposition to undergo an exposure of his testicles to x -rays with the distinct purpose of bringing on sterility. For thirty days he had a daily sitting of ten to fifteen minutes' duration. During the treatment the sperm was examined every eight days. Five examinations were made, and all gave the same result: normal spermatozoa without the slightest change in size, number, or form. No trace of nuclear degeneration or pigmentation was noticed. A sixth specimen was obtained from the patient and exposed directly to the effect of the x -rays, but without the slightest result. After the failure of this method the patient had a bilateral resection of the spermatic ducts done. As according to Albers-Schönberg at the end of six months an atrophy develops gradually in the testicles, Philipp extracted directly from the testicle with a hypodermic needle a few drops of semen. The microscopical examination confirmed entirely Albers-Schönberg's and Seldin's views: no trace of spermatozoa could be found. The testicles diminished in size, but the sexual power remained normal. In another case a man of thirty-one suffered from intertrigo with pruritus ani. X -ray exposure over the perineum was proposed. A daily exposure for ten minutes, and altogether 195 minutes, cured the patient from the intertrigo and pruritus ani. Seven months later a small quantity of sperm was examined and no trace of spermatozoa was found.

Very recently F. Tilden Brown reported his observations concerning the sexual condition of physicians and patients who have been exposed to the x -rays. He announced at the January meeting of the New York

¹ *Münch. Med. Wochenschr.*, 1903, No. 43.

² *Münch. Med. Wochenschr.*, 1903.

Academy of Medicine that "men by their mere presence in an x -ray atmosphere incidental to radiography or the therapeutic uses of the rays, after a period of time as yet undetermined, will be rendered sterile. In the last few days ten individuals who have devoted more or less time to the work during the past three years—none of whom have had any venereal disease or traumatism involving the genital tract—have been found to be the subjects of absolute azoöpermia. None of the number are conscious, however, of any change or deterioration in regard to their potency." In the report of Drs. Brown and Osgood¹ we find similar observations. Within the last three months they observe eighteen cases of azoöpermia or oligoöcrospermia in men who have operated Röntgen-ray tubes for a half to four hours three times a week for the past two to six years.

It is remarkable that similar observations were made upon insects and plants. Seeds, for example, exposed for even a few hours to the action of x -rays, lose their ability to grow.

The action of Röntgen rays upon the female generative organs has also been the subject of special study very recently. Ludwig Halberstaedter² reports the results of his experiments on mammalia. Series of dogs were selected, and exposure to the rays was carried out in the usual manner. Ten or more days later extirpation of the ovaries was performed. Marked microscopical changes were noticed as to size of the organs and to the number of Graafian follicles. As to the latter, the later the examination is made the fewer follicles are found. This was also verified by histological changes. In exposure to mild rays the disappearance of follicles is not as complete as in the experiments with stronger rays. Besides degeneration of the follicles, the microscope also shows a more or less large number of vacuolated spaces which according to the author are perhaps traces of degenerated follicles. The same experiments have also shown that ovaries present a far greater susceptibility to x -rays than the skin, a fact which becomes evident a very short time after the exposure.

The practical importance of all these investigations, both from a personal standpoint and in regard to assistants and patients, is certainly too evident to dwell upon. Prophylaxis in an x -ray atmosphere is of paramount importance; adequate protection to all parts of the body not directly exposed for examination or treatment should be provided. On the other hand, the facts herein set forth give us a convenient, painless and harmless method for rendering a male or female sterile in cases in which sterility must be obtained for serious reasons. Resection of seminal ducts, or removal of ovaries, although more or less safe with the modern surgical methods, are nevertheless inferior to bloodless methods. A patient is far less likely to object to this measure than to mutilation, and it is to be hoped that investigation will continue along these lines.

Pathogenesis—It is yet debatable what particular element plays such an important role in producing lesions during exposure to x -rays. Some believe that it is the ozone which is formed around the tube; others, electric discharges emanating from the tubes; and still others, the x -rays themselves. The latter view is accepted by the majority of writers.

¹ *American Journal of Surgery*, April, 1905.

² *Berl. Klin. Wochenschr.*, January 16, 1905.

It is their direct action that causes the lesions described above. According to Scholz, the x -rays have a specific action on the elements of the skin, causing a slow degeneration of the cells of epidermis, hair-follicles, glands, and also of the connective-tissue cells of the corium; the nucleus is affected by the degenerative process as well as the protoplasm of the cell. As to the question whether the x -rays have only a local or a general effect on all the tissues through which they pass, the consensus of opinion is that the first effect is on the skin; the deeper tissues, as muscles and bones, are influenced only slightly. If necrosis follows, it is only secondary to a pronounced inflammation and ulceration. Curiously enough, they affect not only the skin at the point of their penetration, but also at the level of their exit. Revillet and Kümmler have shown that illumination of the thorax produced an erythema on the thorax and back. As to the intermediate organs the effect is usually little or none whatever. This observation is also in accordance with clinical experience.

Treatment.—There is no special treatment for x -ray accidents. As the superficial lesions are similar to those produced by the violet rays of the spectrum, Bar's suggestion as to the use of red light, which is proven to be antagonistic to the violet, is certainly very interesting. He at least obtained very encouraging results. On the other hand, Kaiser reported recently that blue light-rays gave him good results. Pain may be relieved by static electricity, according to d'Apostoli. High-frequency currents have been also suggested for x -ray burns. As to local applications to the diseased tissues, various drugs have been recommended, but none has any specific value. Nitrate of silver (2 per cent.), picric acid ($\frac{1}{2}$ per cent.), zinc ointment, cocaine (for pain), peroxide (in cases of exudation and suppuration), pyoktanin (3 per cent.), and others, are all remedies which are advised in x -ray burns; but they have been used in burns of any other origin. It is well, however, to remember that the effect of the drugs just mentioned is not as prompt as in ordinary burns.

A few hints concerning special features of the action of x -rays will aid in forming an idea of prophylactic measures. Daily radiation has a cumulative effect. Various parts of the body are differently affected. Parts covered with hair (head and chin), the nails, and bloodvessels, are more predisposed to inflammatory dermatitis than any other portion. A diseased skin is much more easily penetrated by x -rays than a healthy skin. According to Scholz the more rays emanate from the tube, the stronger is the effect on the skin. He also advises the use of soft tubes for therapeutic purposes instead of hard ones, as from the latter emanate few x -rays, but there is much electrical discharge. Large doses, prolonged exposures, and proximity of the tube, are capable of devitalizing tissue-elements and causing their degeneration. An important point to remember concerning the administration of x -rays is the danger of disseminating the malignant process in cases of neoplasms, or of causing a more rapid growth.

OTHER RAYS.

Becquerel's discovery of rays given off by uranium (pitchblende) or its salts led to the discovery of radium and polonium, by M. and Mme. Curie; also of actinium (Debiene), of rays N and N' (Blondlot

and Charpentier). They all possess a highly penetrating power which is not present in ordinary light. Although the therapeutic value of these rays is at present not definitely determined (see above), we know, nevertheless, of damages which are sometimes produced by their indiscriminate use. Welkhöff and Giesel have first shown the deleterious effect of Becquerel's rays upon the skin, namely, ulcerations and necrosis. Similarly to x -rays there is a latent period only after which the lesions begin to appear; the redness appears only a few days after the exposure, the ulceration weeks later. In Curie's case of his own person ulceration appeared fifty-two days after the onset. In Askinass's case inflammatory changes commenced to show themselves thirty days after two hours' exposure. According to Halkin, Becquerel's rays act simultaneously on the bloodvessels and epithelial and connective-tissue cells. V. Henri and A. Mayer have demonstrated the effect of radium on the blood; hæmoglobin is transformed into methæmoglobin, and its solubility is diminished. Askinass and Caspari have shown that Becquerel's and Curie's rays have an inhibitory influence upon the metabolism in living tissue. In this respect their effect is identical with that of x -rays, but their action is more intense and destructive than the latter.

ELECTRICITY.

To Galvani belongs the discovery of animal electricity, in 1786; and Pfaff, Humboldt, Ritter, Nobili, Matteucci, and others, labored in the further development of it. It was reserved for the classic investigations of DuBois-Reymond (1848-1884) to place this part of physiology upon an exact foundation. The electrogenetic properties of animal tissue led to series of discoveries which finally have proven that electricity is an important therapeutic agent. Its utility in various affections of the nervous system is established beyond doubt.

Electricity may under certain conditions produce local and general disturbances and even death. The universal utilization of electrical energy in industry exposes human beings to its deleterious effects to a considerable degree. The numberless accidents caused by electrical currents, and the facility with which they are produced, makes it the duty of physicians to become familiar with these accidents and with the means of removing the consequences. The currents became dangerous only when their energy reached the high degree necessary for industry. Before the invention of the dynamo there were rarely serious accidents. The first cases of death occurred when electricity was applied industrially. Everybody is exposed to the danger of receiving accidental electrical discharges more or less powerful. A rupture of a wire is not an infrequent occurrence, and accidental contact with a wire which has fallen, and in which still circulates a current, is liable to lead to very serious disturbances in the organism.

It is considered that contact with a wire in which circulates electricity of 500 volts is fatal. Resistance of the human body to the passage of a current of this intensity is considerable. It varies with the degree, extent and duration of contact, the state of moisture and thickness of the skin, the state of general health, and whether alcoholism is present or not. In

one case a man in good physical health, whose flannel undershirt was thoroughly wet from perspiration, withstood without ill effects a shock of 2,000 volts. Lowenheim and Jellinek report a case of 5,500 volts which did not terminate fatally; Picon and Leblanc report a similar case. The immediate effect of electrical current may be death, shock with temporary loss of consciousness, painful sensations, and, finally, burns of the skin.

Death.—When an individual is stricken by a fatal current there is a violent tetanic contraction of all the muscles of the body, followed by loss of consciousness. Three or four minutes later the respiration ceases. The mechanism of death, according to Provost and Battelli, depends upon the degree of tension of the current. In high tension (1200 volts or above) there is inhibition of the nervous centres; the respiratory centre is first affected, and the heart ceases to beat only subsequently to asphyxia.

Low-tension currents (not above 120 volts) produce paralysis of the heart, but the respiration continues for a certain time. The heart shows a fibrillary tremor, and as soon as the latter appears the beating is immediately arrested and no more blood is thrown into the circulation. Currents of average tension (240 to 600 volts) produce paralysis of the heart in a state of fibrillary tremor, and an absolute cessation of respiration. We therefore see that the fibrillary tremor of the heart is the most dreaded phenomenon, while the shock of the nervous centres is of no special import. The cessation of the heart-beat is independent of the extrinsic innervation of its muscles. When there is no fibrillary contraction of the heart, there is no danger to life.

The currents used in industry are either continuous or alternating. Both cause shock or death by the same mechanism. It is interesting to note that the continuous current requires a higher voltage than the alternating current to bring on a paralysis of the heart. On the other hand, the inhibition of the nervous system is more pronounced with continuous than with alternating currents.

Other Consequences of Electrical Shock.—If death does not ensue, in ordinary conditions the sudden contact with an electrical conductor will produce syncope, which is usually of short duration. The reestablishment of normal functions may be complete and rapid, but sometimes the various nervous disturbances may remain very tenaciously. In the latter case there is usually a state of hebetude for several days, accompanied by weakness, headache, and sometimes palpitation of the heart. In some cases there was a state of mental confusion or delirium, tremor, and a general depression of the nervous system similar to that following traumatism. Psychoses were observed by Bucknill, Tuke, Sanze, Pick, Cipriano, Lahnson, and others; but the mental disturbances were all transient in character. Amnesia was reported by Heusner, Ebertz, Winiwarter, and others. Painful sensations, more or less pronounced, in the muscles and in the thorax have been recorded in a number of cases as of frequent occurrence.

Besides these immediate disturbances, there are quite a number resembling well-defined nervous affections. Functional nervous diseases, as hysteria and neurasthenia, are common occurrences after an electrical shock. Nothnagel, Gibier de Sarigny, and Charcot, contributed considerably to the subject. Abundant examples of either of these two

neuroses, or of a combination of both, are found in recent literature. One of the most typical cases of hysteria was observed by the writer in a woman who was touched at the elbow by an electric wire which broke while she was walking on the street. A complete hemianæsthesia to touch, pain, and temperature, covering also the face, pharynx, conjunctiva, ear, and head, was present in this case; the visual field was markedly contracted on the same side. She was seen by the writer shortly after the accident and kept under observation during two years. The above sensory disturbances persisted in spite of complete recovery from the immediate effects of the electric shock. Another young woman was struck by lightning while sitting near an open window. She was seen by the writer after she regained consciousness, *viz.*, about an hour after the shock. She developed typical hysterical paroxysms; suddenly she would fall, being seized with a slight tremor in the extremities; a minute later the trunk would begin to assume various positions, opisthotonos being the most frequent. At the same time the patient would scream, or laugh loudly, or cry. The seizure would last ten minutes. At first the attacks were very frequent, averaging five or six a day. A month later they began to disappear gradually, and at the end of three months she was entirely free from them.

Epileptiform and apoplectiform seizures were reported in old and recent literature. Smurthwaite¹ observed a case of general convulsions in a laborer who accidentally came in contact with a current of 2,150 volts, and who completely recovered. Batteli² made a special study of the continuous and alternating industrial currents with a comparatively low voltage (120 to 240 volts). He observed that when one electrode is placed in the mouth or nostrils and the other on the neck, the heart is not affected, the nervous centres alone being excited. With this arrangement an epileptiform convulsion makes its immediate appearance as soon as the current is closed. A contact of $\frac{1}{20}$ of a second is sufficient to bring on an attack; the latter becomes very violent if the duration of the contact is prolonged to $\frac{1}{10}$ or $\frac{1}{5}$ of a second. The attacks present the typical tonic and clonic contractions of the muscles, with froth at the mouth and dilated pupils, followed by the usual comatose state. Bulbar symptoms, transient in character, were reported in a few cases, but in view of their temporary nature they were probably cases of functional neuroses. However, Charles K. Mills reported two cases observed by him personally in which there cannot be any doubt of the organic character of the involvement of the medulla.

There are also in the literature records of apparently undoubted cases of hemiplegia, spastic paraplegia, and of disseminated sclerosis, following lightning or shocks from other electric sources, but all these records are only clinical. The pathological findings of those few cases that came to autopsy are in general negative, except a few capillary hemorrhages or small cellular changes in some cases. Congestion of brain and cord was found in some cases (Kratter). Our knowledge, therefore, of the supposed organic cases is extremely unsatisfactory.

Eye disturbances have been observed by various authors. Dimness of vision, ptosis, contraction of pupils, sluggish reflex reactions, subcon-

¹ *British Medical Journal*, 1901.

² *Société de Biologie*, 1903.

junctival ecchymoses, cloudiness of cornea—these are the external ocular changes reported. In a certain number of cases profound alterations of the eye were noticed, *viz.*, apoplectic hemorrhages in the retina, with pigmentation, tearing, bleeding, and rupture of the choroid, iridocyclitis, luxation of the retina; anæmia of the optic nerve, optic atrophy, and blindness. Fuchs, Knies, Meyerhofer, Priendisberger, and Vossius, report the formation of cataract. Hess observed, experimentally, cataract formation in animals. Disturbances of the auditory apparatus occurred in many cases. Pain in the ear, with difficulty of hearing, are frequent symptoms following electric shock. The writer recalls a case of absolute deafness in a man of twenty-five occurring after having been shocked by lightning. In this case there was loss of consciousness and a partial hemiplegia on the left side; but the deafness was complete in both ears. Only one month later improvement in hearing appeared. The patient recovered entirely. Clark, Ludewig and others report tears of the drum. Kayser and Freund report permanent deafness from paralysis of the eighth nerve, with or without simultaneous perforation of the drum. Gognel observed hemorrhages from the ear.

Burns.—A conductor charged with electricity will produce burns in living tissue when it is brought in contact with the latter. Radiation of electric light may produce some superficial burns, but the appearance of the burns and the accompanying general symptoms are different when electricity has a direct effect on tissue from immediate contact. The effect of a current is not always in direct relation with its strength, as sometimes currents of 5,000 volts produce only superficial burns, and of 500 volts deep burns. Individual circumstances accompanying the accident—duration and degree of contact, dampness of skin, the degree of cleanliness of the latter—all are of great importance as to the effect of the contact.

In electrical burns all the tissues, from the epidermis to the bones, may be affected. They may be superficial or deep. They are usually not limited to the dermis; the muscle and bones are also affected. The loss of substance may be small, or may invade a portion of the limb. Immediately after the contact the skin becomes black, and the affected portion is soon covered with a hard layer resembling parchment. During the process of reparation the wound acquires a red and smooth surface. There is never present at the periphery that whitish ring which is found in ordinary burns. Electrical wounds never suppurate and are never moist; the parchment-like layer is preserved until a new epidermis is formed. The characteristic feature of electrical burns consists in their absolute painlessness during the entire process of healing. The duration depends upon the degree of the burns; so that, when the bone is involved, the course will be prolonged and complications will set in. Superficial burns heal up entirely and rapidly. In deep burns gangrene may occur and necessitate amputation of the limb.

Burns may be accompanied by a nervous shock more or less serious, frequently by syncope. The latter may be fatal and the patient dies in a few minutes despite all possible care. We said above that from a tension of 500 to 600 volts upwards, electrical accidents may be fatal. It is to be noted that the voltage alone does not determine the question of death. Perhaps the danger lies in the fact that an electrical burn forms a bad contact by interposition of gaseous products between the tissue and the

metallic conductor. The histological changes of electrical burns are identical with those of *x*-ray burns. (See section on *X-RAYS*.)

Treatment of Accidents Produced by Electricity.—When the person is still in contact with the conductor, an effort should be made to form a short circuit, by means of a body which is considered a good insulator, as a piece of wood. If there is no object at hand, we should free the victim by giving him a push with the foot; the person that touches the victim will feel but a slight shock, because the resistance of the shoes is great. After the contact is interrupted, recovery usually follows if there is no loss of consciousness. If consciousness is lost respiration may continue or else be arrested. In the first case the ordinary means usually employed in syncope should be applied, as traction of the tongue, flagellation, friction, cold water, etc. In the second case it is advisable to institute artificial respiration at once, if the heart continues to beat. In case the heart is in a state of fibrillary tremor, artificial respiration is useless.

Burns should be treated on general principles. The affected limb should be immobilized; protection of the wound with sterilized gauze is usually sufficient. In cases of extensive burns, skin-grafting is indicated.

CHAPTER III.

AIR.

By ALFRED GORDON, M.D.

PHYSIOLOGICAL EFFECT OF AIR.

AIR is a mechanical mixture of oxygen (21 per cent.), nitrogen (79 per cent.), water-vapor, small quantities of carbon dioxide, and traces of ammonia and peroxide of hydrogen; also organic matter. The most vital element, without which life is impossible, is oxygen. Priestly, its discoverer, recognized the enormous importance of this gas for life; it is a life-sustaining element, of which an adult consumes one-half of a cubic inch at each inspiration. Its activity in life is regulated by nitrogen. In respiration free oxygen is taken up by the living substance and in return carbonic acid is given off; hence combustion (Mayo) (*viz.*, oxidation) takes place. Without the process of oxidation, metabolism (*viz.*, life) cannot exist. This is true in regard to individual cells, tissues, organs, and the entire organism.

In normal condition there is a certain output of CO_2 and intake of O . As soon as the equilibrium is interrupted, as for example an excess of CO_2 and deficiency of O , the organism will be disturbed; and if this is carried to a higher degree of difference, a diseased condition will develop with more or less persistent symptoms; and even death may ensue.

PATHOLOGICAL EFFECT OF AIR.

CO_2 , or the gas which we exhale, is an obnoxious element, and may become even dangerous if it is present in excess. It is a familiar fact that in assemblies behind closed doors after a certain time one feels uncomfortable, and may develop a sense of weight, uneasiness, or pain in the head, dizziness, or ringing in the ears; sometimes vomiting, disposition to sleep, difficult respiration, rapid loss of sensibility; and at times syncope. This symptom-group is mainly due to excess of carbonic dioxide (CO_2). In this condition exhalation of vapor should also be taken into consideration.

Atmospheric humidity is as essential to the life of organized beings as oxygen itself. Tyndall says that the vapors of water interfere with the rapid ascent of warm air, which without this protection would have been lost for us. The vapors become warm, envelop the earth, and protect its surface from becoming cold.

The action of humidity on the organism is very important from the standpoint of respiration and the function of the skin. In dry and warm air the cutaneous evaporation is very active; in dry and cold air the pulmonary evaporation is stimulated. The humid and cold air presents this inconvenience, that by diminishing cutaneous evaporation and increasing the loss of heat from the surface of the body, it predisposes to catarrhal affections, to renal diseases, and to rheumatism. The humid and cold air diminishes the cutaneous evaporation, and when perspiration is not evaporated the variations in the temperature are apt to cause diseases which are usually attributed to cold. Besides, the appetite and metabolism in general suffer and disable the affected individuals for any work; intestinal diseases develop easily, and pulmonary tuberculosis finds a favorable condition for its rapid development. Moist and warm air has a special affinity for organic matter, and therefore predisposes to development of pathogenic organisms, which makes the surrounding atmosphere insalubrious.

If the inhalation of impure air is prolonged or constant, as, for example, in unclean dwellings, etc., malnutrition and anæmia, with gastro-intestinal disorders, will be the consequence. These factors play a predisposing role in pulmonary diseases, especially in tuberculosis. Sewer air is characterized by diminution of oxygen and increase of carbon dioxide (more so in summer), and association of ammonia compounds with hydrogen sulphide. All these elements are undoubtedly obnoxious, but what particularly makes the sewer air unwholesome is the association of organic matter, which is an excellent carrier of pathogenic microbes. It is readily understood that some infectious diseases may be directly traced to this origin, especially during epidemics.

The disturbance in the proportion of the normal constituent elements of air is observed not only in association with organic material subject to putrefaction, but also in changes of *atmospheric pressure*. In normal conditions there is an antagonism between the internal pressure and the pressure produced by the surrounding atmosphere. Equilibrium is maintained when one counteracts the other; but should local atmospheric disturbances make their appearances, air pressure is felt.

We have seen above that oxygen is indispensable for life, and the purity of air is judged by the presence of a sufficient amount of this gas. If oxygen is conducive to health, it may under certain conditions become obnoxious and cause a pathological state. The latter is precisely observed in changes of atmospheric pressure. Paul Bert says pure oxygen may act as a poison, and animals die in ordinary air when pressure of O falls to 3.4 per cent. of atmosphere, while in superoxygenated air they die when pressure of CO₂ rises to 25 per cent. of atmosphere. In order to collect facts regarding the effect of various degrees of air pressure on human life, investigators employed the method of balloon-travel. The first trip was made in Paris in 1875, by Spinelli, Sivel, and Tissandier. They rose to a height of 7,000 meters. At that level they felt a constantly increasing weakness and apathy until they reached a complete absence of power of motion, although their mentality remained unchanged. Soon they could not use their tongue for speaking. At the height of 8,000 meters they all lost consciousness. Tissandier regained consciousness and survived, while the other two perished. The principal facts noted in

both fatal cases were bleeding from the mucous membranes of the mouth and lungs, accompanied by extreme lassitude and temporary paralysis of the respiratory muscles, which proved fatal.

Since the famous ascension, which has been followed by many others, we have learned the effect of rarified air on the human organism. On the other hand, we know that travelers experience disagreeable symptoms when they climb mountains. Alterations of atmospheric pressure have been regarded by some as coincident with pulmonary congestion and with neuralgic and rheumatic pains; but a well-defined symptom-group due exclusively and directly to altered air pressure we find in: (a) *mal des montagnes*; and (b) *caisson disease*.

Mountain Sickness (*Mal des Montagnes*).—The physiological disturbances experienced on altitudes have been known since the fifteenth century when Da Costa described them under the name of *mal des montagnes*. His first description has been verified and corroborated by many savants since, so that at present the condition has a clearly defined symptom-group. At the height of 3,000 to 4,500 meters the first noticeable symptoms are palpitation of the heart and rapid pulse. Soon the respiration becomes accelerated; the patient becomes restless, cannot sleep, and sometimes has vomiting-spells. There is more or less pronounced pain in the knees and legs. Walking is difficult, and the patient feels exhausted. At the same time thirst increases the suffering. The tongue is dry; the appetite is lost; nausea and eructations torture the patient. In extreme cases hemorrhages may occur which are followed by syncopal attacks. The hemorrhages are most frequently from the mucous membranes of the air passages. Lazarus also observed cyanosis of the extremities when a height of 7,000 meters is reached. The symptoms are therefore analogous to those of ascent in a balloon, but it is remarkable that in the latter case the effects of diminished pressure are not felt until twice the height has been reached. The reason of it lies in the wasting of considerable muscular energy in climbing. The wasting is accompanied by a larger loss of calories than the organism can supply, as the respiratory combustion cannot furnish a sufficient amount of heat because of low density of the air. The body temperature falls below normal and the ascent becomes difficult. Consequently in *mal des montagnes* we have two factors: the effects of rarefaction of air and those of fatigue.

The effects of *mal des montagnes* are not uniform in various individuals and at various heights. They depend upon the age, habits, antecedent health, etc. At 3,000 meters the symptom-group is present in every case. Passive movements can be produced in healthy individuals without marked effect in their health even at the level of 4,000 meters. Active movements even at a lower height will produce the symptoms enumerated above. This observation is a sufficient hint for preventive measures. In addition to the latter, care should also be taken not to remain in the rarefied air longer than two to three hours.

When a more or less prolonged sojourn in mountainous regions is taken up by persons who come from lower altitudes, they become subject to the following symptoms, which are particularly marked when the barometer stands low: hemorrhages and bronchial and nasal catarrhs. Attacks of hæmoptysis are often seen in tuberculous patients who come to high altitudes in search of health. Epistaxis is observed in perfectly healthy

individuals. The catarrhal trouble is quite frequent and rebellious to treatment. W. H. Gardner¹ describes a curious symptom-group observed on himself. Besides the usual symptoms described above, he developed a confusion of ideas and a paretic condition on the entire left side of the body, including the tongue, so that he could not articulate; he also felt a throbbing in the carotids, and his pupils were dilated. He describes several cases, in one of which he also observed hemianæsthesia followed by epileptiform convulsions on the same side; in other cases he observed apoplectiform attacks with or without aphasia. The same author speaks also of "rheumatism," which is exceedingly common not only among persons who have recently come to, but also among the inhabitants of, mountainous regions.

Pathology.—As to the pathogenesis of the affection, several theories have been advanced. Some believe that, in view of the fact that the symptoms are analogous to the physiological and pathological effects of ozone, and that ozone is more abundant the higher the level of atmospheric air is considered, for these reasons it is probably the direct cause of *mal des montagnes*. Others believe that the lowering of air pressure produces a congestion of inner organs, or circulatory disturbances. Paul Bert has shown that the cause of the disturbances lies in the diminution of oxygen in the inhaled air, and that the symptoms can be entirely removed by inhalations of oxygen. The latter view is the most accepted, as the majority of the symptoms can be readily explained. In fact, the accelerated respiratory and circulatory movements have for their purpose not only a larger absorption of oxygen, but also the removal of carbon dioxide. But the exhalation, although very active, is not longer sufficient for maintaining the normal composition of the blood, which is saturated with CO₂. In this fact lies the reason of the headache, the nausea, the irresistible insomnia, the low bodily temperature, and other symptoms observed in travellers on mountains. The treatment, therefore, consists of supplying the gas which is wanting. Gardner suggests, that in view of the difficulty of furnishing the inaccessible mountainous localities with oxygen, its administration through the stomach is beneficial. In his hands chlorate of potash was very useful.

Caisson Disease, or Diver's Paralysis.—Above, we considered the effect of rarefied air on human economy. If the condition is reversed—*viz.*, if the organism is subjected to a high atmospheric pressure—the morbid manifestations will be almost exclusively confined to the nervous system. The symptoms observed in divers or workers in caissons will appear only after they return to the surface. It is therefore the lessened atmospheric pressure which is the immediate cause of the disorder of the nervous system. Nevertheless, as this lessening follows the increased pressure beneath the surface, it is the latter that is primarily at fault.

The effect of rapid changes of barometric pressure was observed for the first time by Trizus, in 1839, on men working in cylinders with compressed air; and in 1854, by Pal and Watelle, on miners. Later other contributions were put on record; but they all have reference to the clinical side of the subject. The first complete description of pathological find-

¹ *American Journal of the Medical Sciences*, 1876.

ings which threw some light on the pathogenesis of the affection and could explain the clinical manifestations was given in 1879, by Leyden.¹

Symptoms.—Shortly after the return to the surface and after a prodromal stage consisting of pain, more or less severe, in the large joints, and also in the epigastrium and sometimes over the entire body, a paralysis occurs. The most frequent form of this is paraplegia, but sometimes hemiplegia is observed. The onset and the character of the paralysis is very similar to that of transverse myelitis. If we take into consideration the frequent involvement of the sphincters (retention and constipation), and the sensory disturbances, the resemblance to myelitis will be complete. All these symptoms may present variations in degree; in some cases the loss of power is only partial, in others more or less pronounced, and in still others absolute. Also both extremities may not equally be involved in regard to motor power as well as to sensations. In some cases, in addition to the myelitic symptoms there are also vertigo, headache, vomiting, slight confusion, convulsions, and double vision. Prostration is present in more severe cases. In fatal cases, deep coma, irregular respiration, and symptoms of cardiac paralysis, announce approaching death. As an occasional occurrence we may mention small perforations of the ear-drums, which are due to the pressure either externally or from within outward.

Prognosis.—Generally speaking, recovery occurs frequently. In complete paralysis the loss of power may last only a few days. In severe cases the power may never return and the victim will remain permanently crippled. Death in protracted cases results from the same causes as in chronic myelitis; namely, from suppurating bed-sores, cystitis, pyelitis, etc., or from an intercurrent disease. On the other hand, death may occur shortly after the onset as in acute myelitis. The hemiplegic form of paralysis bears usually a favorable prognosis. Deep coma with irregular respiration is usually a bad omen.

The degree of damage and consequently the probabilities of recovery depend in a general way largely upon personal predisposition, previous health (condition of heart, bloodvessels, kidneys, etc.), habits (alcoholism), age (fifty years is considered the maximum), upon the length of time spent in the caisson under high pressure, and finally and mainly upon the manner in which the diver is brought to the surface. That is to say, the less rapid and abrupt the decompression of air is done, the less damage the nervous system undergoes and the more chances for recovery there are. In the remarks on treatment this question will be discussed.

Pathogenesis and Pathology.—The authors are divided in regard to the explanation of the symptoms. There are only two theories in vogue at the present time. According to one of them, the so-called gaseous theory, the blood while under high pressure becomes overcharged with gas (oxygen and carbonic acid), and the longer the exposure the greater the amount of gas. When the surface is reached, the gas attempts to escape through the lungs, but this can be done only gradually and progressively. In the meantime the superfluous gas circulates in the blood in bubbles, and may either form emboli or escape through the vessel-walls into the surrounding tissues and consequently produce considerable pressure.

¹ *Arch. f. Psych.* IX. S. 316.

If during this time the lungs will continue to remove gradually some superfluous gas, the air of the tissues may become gradually reabsorbed and thus relieve the pressure. This is precisely what is observed in the majority of cases; at first paralysis with the associated symptoms, and then their gradual disappearance. The reason of the special effect of this mechanism on the nervous system lies in the fact that the latter (brain and cord) are situated in cavities which to a large degree are hermetically closed. The spinal cord suffers the most, as, besides the cause just mentioned, its return circulation is very slow because of the large number of plexuses. There are a number of facts, particularly experimental, which are in accord with this theory. It is sufficient to recall the experiments of Hoppe Seyler, in 1855, and Paul Bert, in 1872 and 1873, in which sudden changes of atmospheric pressure produced the presence of a considerable amount of gas-bubbles in the blood.

According to the other view there is a congestion followed by a stasis. The high pressure drives the blood from the periphery to the internal organs, especially to the nervous system. The bloodvessels of the latter, unlike those of other organs, have no support from counter-pressure, and therefore remain dilated. A paralysis of the vessel-walls follows. When the atmospheric pressure is diminished, and consequently the blood-pressure relieved, the paralyzed vessels cannot follow, and stasis of the brain and cord will be the result.

While both theories are tenable, and apparently do explain all the symptoms of the affection, it is nevertheless difficult as yet to tell which of the two has the more solid basis. As to the pathological findings, there are only a few cases on record with necropsies, and unfortunately their descriptions are incomplete. In those important cases which could throw much light on the subject, the cord was unfortunately not examined microscopically.

The latter are the cases which ended fatally soon or immediately after the patients were brought to the surface; they are the genuine divers'-paralysis cases. The most constant microscopical changes found in almost every case are congestion of brain and cord and internal organs in acute cases, and softening in chronic cases. In the incurable cases of long standing in which the condition remained permanent until death, lesions of typical chronic myelitis were the usual findings. A typical example of such a condition can be seen in Fr. Schultze's case.¹ There was a complete paraplegia twenty minutes after the diver left the caisson. Pain, decubitus, and cystitis, complicated by pyelitis, completed the myelitic picture. The patient lived two and one-half months. On autopsy yellow spots were found in the posterior and lateral columns of the thoracic cord. Ascending and descending degenerations were traced. The bloodvessels showed cell-infiltration in the perivascular lymph spaces. There were also degenerated portions in the gray substance on one side of the cord.

Treatment.—The management of well-developed symptoms of myelitis indicating a permanent and definite lesion of the cord, must be conducted on the same principles as in myelitis. When the symptoms are only commencing to appear, it has been found that with an immediate

¹ Virchow's *Archiv.*, 79 Bd. S. 124, 1880.

return to the surface, or by subjecting the individual to increased atmospheric pressure in any manner at all (pneumatic cabinet, etc.), the symptoms may disappear. It would be a matter of importance, if not of absolute necessity, to have on hand an apparatus in which the patient could undergo high-pressure séances.

Preventive measures constitute the most important part of the treatment. Bad physical health, diseases of the kidneys or heart, alcoholism, obesity, and, finally, hunger, are all contra-indications for subjecting one's self to the high atmospheric pressure. As to the limit of time which is permissible to spend in the caisson, Collingswood's rule is particularly to be recommended. For the first exposure only one hour; for those who are accustomed to the work the number of hours should decrease as the number of atmospheres increase, as, for example, three hours in four atmospheres, four hours in three atmospheres, etc. The locks with which the caissons are supplied, and in which the pressure is gradually reduced, should be used very frequently, according to Smith,

CHAPTER IV.

HEAT AND COLD.

By ALFRED GORDON, M.D.

EFFECT OF TEMPERATURE, TROPICAL AND COLD CLIMATES.

In the preceding sections we have seen that light and a certain chemical or physical condition of air are indispensable to life. Besides these conditions, upon which metabolism directly depends, certain dynamic requirements must be fulfilled if life is to be maintained. Among them is the temperature of the air within certain limits.

The activity of chemical phenomena of living tissue undergoes considerable modifications as soon as the temperature of the tissues is subjected to variations. The temperature limits in which life can exist are of course very different for different organisms. It is well known that a man can resist great variations of temperature. This is probably due to the fact that his internal temperature remains unchanged. However, this natural tendency in maintaining the central temperature unchanged does not go on without certain disturbances in the functions of certain organs. If, for example, the external temperature increases, there is a diminution in the production of CO_2 , the respiration becomes accelerated, and the skin perspires profusely; all the secretory organs eliminate excessively; the nervous system is irritated. If the elevation of temperature is only temporary, the related functional disturbances will be transitory. When the action of heat is prolonged, local as well as general symptoms will make their appearance.

Heat.—The effect of heat must be considered from three standpoints: (1) Immediate contact of living tissue with a hot object; (2) effect of solar heat (see sunstroke and sun-traumatism); (3) effect of hot climates.

Solid or liquid objects, and gas and vapors, when their temperatures are elevated, will produce burns on coming in contact with living tissue; local destructions of skin and mucous membranes will be the consequence.

Fluids, when they do not reach a temperature of 100° , produce only a slight erythema. Water boils at the temperature of 100°C. ; salty water and oil must have a larger quantity of calories and are therefore to be feared. Burns of mucous membranes of the rectum and vagina occur when very hot enemas or injections are administered. Œdema of the glottis may be the consequence of burns of buccal, pharyngeal and œsophageal mucous membranes. Caustic fluids taken by mistake or in attempting suicide lead to very grave injuries of the mucous membranes.

Solid objects, especially metals at a red heat, produce deep lesions; but the burn is confined to the point of application if the substance is not adherent. *Gas* causes accidents through its flame. Those whose work exposes them to explosions (chemists, miners, etc.), are frequently victims of burns; their clothing takes fire and cannot be separated from the body; the skin becomes carbonized and the subcutaneous fat burns; the consequences may be very serious. *Hot vapors* are particularly obnoxious. Droplets of hot water accumulated on the skin will burn it, but they may be also inhaled and penetrate the mucous membranes of the larynx and lungs.

In *burns* we meet with all degrees of active hyperæmias and formation of oedema, hemorrhages, and necrosis in the skin. Since Dupuytren, it has been generally accepted to consider six degrees of burns. The first degree is characterized by *redness, pain, and tumefaction*. The pain is pronounced at the beginning. The swelling is of short duration. The symptoms are transient, and desquamation of the epithelium takes place. In the second degree the Malpighian layer is affected. The epidermis is elevated by vesicles. When the latter are ruptured and the epidermis is removed, granulation and suppuration are found on the underlying layer, which is extremely painful. Deformed scars will always form, if the epidermis is removed. It is therefore advisable to leave the epidermis in place. The third degree is characterized by destruction of all the superficial layers of the dermis. The vesicles, which are large, do not contain a serous fluid as in the preceding degree, but a dark bloody fluid. Sometimes dry, dark or yellow scabs are formed. The pain is exquisite, especially on the sixth or seventh day, when the scab falls off. The latter leaves a granulated and suppurating surface which is replaced later by a deformed cicatrix. In the fourth degree the destruction of the skin is complete; even the subcutaneous cellular tissue is affected. The scabs are here more or less large, dark, and dry. Pain is not pronounced, because the nerve-ends are destroyed. The gangrenous layers fall off and cause sometimes an inflammatory condition. The cicatrices are formed very slowly and are very irregular. In the fifth degree we often find destruction of skin, muscles, bloodvessels, and nerve-trunks. When the scabs fall off, sometimes articular cavities are laid open. When the gangrenous tissue falls off, purulent arthritis, visceral inflammation and abundant hemorrhages may occur. In the sixth degree all the tissues are carbonized, the periosteum is destroyed, the bone is necrosed, and an entire limb may be lost.

In addition to local symptoms there are frequently general phenomena more or less pronounced. They depend upon the extent of the lesion. When the burn is grave, the pain may be so intolerable that the patient falls in a stuporous state. He is somnolent, does not speak or move; the face is pale; the skin is covered with a cold perspiration; the temperature goes down below normal; the pulse is imperceptible; and the respiration becomes irregular; anuria may occur. In another series of cases with the same lesions the general condition is of a diametrically opposite character; extreme excitement with delirium and convulsions will be observed. In a certain number of cases there is a marked elevation of temperature, which is due to visceral inflammation. Here we observe loss of appetite; constipation, or else a diarrhœa; generalized bronchitis, bron-

chopneumonia, or pleurisy. The kidneys may become involved, and albumen is found in the urine. Finally, cerebral congestion, with exudation in the ventricles, has also been observed.

During the period of disappearance of the scabs the suppuration described above is always accompanied by general symptoms. In pronounced cases amyloid degeneration of the viscera may occur and lead to cachexia and death. In other cases new infections may occur in the suppurating wound: erysipelas, septicæmia, secondary hemorrhages, and tetanus may develop.

Pathology and Pathogenesis.—The common findings are congestion of the digestive and respiratory tracts and of the nervous system. But the complications cited above will add other lesions independently of burns. As to the pathogenesis of burns various views have been advanced, and among them the ideas of Metchnikoff's and Ehrlich's schools are the most acceptable. In burns there is complete or partial destruction of the cell-elements of the blood; this has for consequence formation and absorption of cell poison (hæmotoxin). In extensive burns we have to deal with destruction of a greater number of cells, and therefore with a larger surface for absorption of the products of this destruction. Capillary emboli, thrombi, and infarcts, especially in the kidneys, are of frequent occurrence; they explain the cases of sudden death so frequent after extensive burns.

Prognosis.—It depends largely upon the extent and depth of the burn and upon the importance of the affected organs. A lesion which would be insignificant on the skin will be of paramount gravity if it occurs in the throat, as œdema of the glottis may ensue and be followed by death. On the other hand, a burn of second degree, if it is extensive, may be more serious than one of the third or fourth degree which is less extensive. The complications play a great role in the course and termination of a burn.

Treatment.—In burns of the first degree, sedatives for the pain and external applications of liniments containing cocaine or morphine are sometimes sufficient. Prolonged baths at a temperature slightly lower than the body temperature are particularly recommended. In burns of the second degree one must not remove the epidermis raised by the vesicles. The latter should be punctured at its lowest point. If, however, the epidermis is accidentally removed, the burn should be covered with a thick layer of antiseptic cotton. Cotton is a good filter for air, protects the nerve-ends, and lessens the inflammatory condition by pressure. In case the cotton is moist with exudation from the wound, it must be changed. It should remain in place until a new epidermis is formed. When the burns are deep and scabs are formed, care should be taken to avoid formation of irregular cicatrices. Antiseptic dressings, and particularly carbolyzed vaseline, or iodoform incorporated in vaseline, and also gauze saturated with a weak solution of sublimate and protected with oiled silk, are all of value; they prevent extensive suppuration with its usual complications. In some cases it is extremely difficult if not impossible to avoid deformed cicatrices; deformities about the mouth, eyelids, nostrils, have been reported. Syndactylism was also observed in cases in which the nude surface of one finger was in contact with the next finger. Similar adhesions have been observed between the arm and thorax. In such cases

grafting of skin will be of great service. In extreme cases, when the destruction of the skin or of a portion of a limb is so great that the function will be hopelessly disturbed, amputation becomes necessary.

As to the general symptoms accompanying burns, they must be treated on general principles. For depression use stimulants; for excitement and pain, sedatives. Good nutritious food should always be given.

Hot Climates and Health.—A question of great practical importance is the morbid effect of hot climates on health. If an individual from a moderate climate is thrown accidentally or otherwise into an atmosphere with an elevated temperature, what will be the effect on his health? The first symptom noticeable will be increase of perspiration. This is followed by a low arterial tension. The urine is reduced. While the lungs expand, the number of inspirations is reduced, and as hot air contains less oxygen than cold, the general metabolism is diminished. The tolerability or intolerability of hot air is always associated with humidity. Atmospheric humidity interferes with free evaporation of sweat, and this necessarily interferes with the mechanism concerned in heat generation. A diminution of capacity for intellectual work—with a condition of languor and general weakness, loss of appetite, disturbance of digestion, of respiration, and of circulation, are the usual symptoms observed in individuals who come from a moderate climate to reside a more or less prolonged period of time in tropical countries.

There are certain diseases that are most common in the tropics, such as malaria, yellow fever, beri-beri, dengue, cholera, dysentery, leprosy, hepatic abscess, and others. This is probably due to the fertile ground which certain bacteria find in heat associated with humidity. On the other hand, hot air with moisture predisposes to various affections, as intestinal diseases, bronchitis, and meningitis. The latest reports on mortality in tropical climates show that there is a special group of diseases which predominate and are highly fatal. They are nervous diseases, and convulsions in children. According to V. Harvard¹ the mortality from nervous disorders is nineteen per thousand. Sleeping sickness, (produced by trypanosoma), cachexia (caused by ankylostomum), leprosy, and hepatic abscess, are, according to the same author, causes of high death-rates in hot climates.

Cold.—Similarly to heat, the effect of cold varies with the age, with the state of general health, with constitutional diseases, fatigue, alcoholism, and, finally, upon the degree of cold. We will consider here, first, the local effect of cold, and then its general effect.

The effect of extreme cold upon the portions of the body which are exposed (feet, hands, ear, nose) presents three degrees. In the first degree there is a dark redness of the skin. The circulation is poor, the stagnation of the blood in the peripheral capillaries leads to infiltration of the subcutaneous tissue, and the skin is thickened. When the skin is exposed to heat, tingling and itching will be present. Generally the condition does not last long. In some cases it may become chronic. The second degree is characterized by ulcerations. In acute forms they appear at once. The epidermis is raised by a serous or bloody fluid; the thin membrane becomes detached, and an ulcerated surface is seen. In the chronic form

¹*American Medicine*, 1905.

the skin, which is infiltrated, bursts, and the yellow-brownish fluid turns into crusts under which pus is accumulated. The third degree is characterized by death of the dermis and sometimes of the other underlying tissues. Elimination of necrosed tissue begins very soon. If it is moderate, the sloughing will leave a bleeding, ulcerated surface, under which is sometimes found diseased bone.

Pathology and Pathogenesis.—Laveran and Cohnheim have studied the effect of cold, and found the bloodvessels to be the main tissue involved. The action of cold consists in narrowing the lumen of the bloodvessels, which may go even to its complete obliteration; the blood does not circulate and the involved area becomes white. Soon the capillaries dilate so that the circulation is slow and sometimes arrested. Thrombosis is the usual consequence, and small emboli may be detached and thrown into the general circulation. Changes in nerves are sometimes very pronounced; ruptures of the vasa nervorum and interstitial hemorrhages have been observed. Laveran and Tillaux speak of fatty degeneration of the myelin sheath, a fact which will explain muscular atrophy, pain, and trophic ulcers, with anæsthesia of the skin. The inflammation of the neuritis may sometimes ascend to the cord. Other lesions were observed. Mathieu and Gubler speak of visceral congestion caused by capillary emboli; Laveran, of loss of mobility of leukocytes.

Prognosis.—The first and second degrees may run their course without general disturbances. However, in soldiers who suffer hardships, in aged people and cachectic individuals, œdema of the face and of eyelids, and albuminuria, were observed. Weak individuals, old people, children, those who overfatigue themselves, those who do not eat enough, those who use alcohol to excess, are all very readily predisposed to the effects of cold, and in such cases the prognosis is therefore always serious. During the stage of suppuration general septicæmia may occur. Recovery is usually slow; the cicatrization is very sluggish, and may be arrested from the slightest cause. This is particularly true in regard to individuals of lymphatic nature.

Treatment.—Prophylactic measures are of utmost importance. The extremities (hands and feet) should be well protected. Sudden changes of temperature should be avoided. Dry astringent friction and massage are recommended.

When the first degree is present, the congestion of the skin will be relieved by washing it with a stimulating fluid (alcohol and others). When ulcerations make their appearance, they should be protected from infection. The third degree requires special attention. The greatest precaution is necessary to avoid extension of the inflammation. The old well-known friction of frozen limbs with snow or with very cold water is not to be neglected. In case of apparent death artificial respiration is indicated. There are cases on record showing that individuals after having remained under snow for several days could be brought to life with artificial respiration. It is therefore important to have recourse to it in every case.

Under normal conditions a temperature which is not very low will produce rather an agreeable sensation; one feels more active, and the respiration becomes better. There is more oxygen taken in and more carbon dioxide exhaled. When the temperature is very low, and the organism

is exposed to it for a long time, functional disturbances make their appearance. At first the circulation becomes more active, and the temperature rises; but soon this excitation disappears, the limbs become numb, and the sight impaired. A general lassitude and an imperative desire to sleep make their appearance; general sensations become obtunded, respiration is difficult, the heart rate is slow, and syncope, followed by death, may ensue. There are, however, cases on record showing that individuals remained four, six and even eight days under snow and nevertheless continued to live.

Before death occurs, the muscular fibers cease to contract voluntarily; the muscles of the neck and of the extremities become rigid, and thus immobilize the body in a position which it had assumed at the time it was overtaken by cold. This explains the bizarre attitudes in which the bodies of individuals who died from extreme cold are found. According to Desgenettes, muscular contractures may spread over the entire body, and epileptiform seizures may carry off the unfortunate victims. It has been also observed that in a certain number of cases the cold air entering the lungs produced excruciating pain and sudden arrest of respiration. In some cases there is a state of delirium, with a tendency to suicide.

The degree of cold which is apt to cause death is difficult to determine, because there is a considerable difference in resistance in various individuals. A man in perfect health is capable of tolerating a very low temperature which an individual in a state of fatigue or exhaustion is unable to resist. In Tagetthoff's "*Le tour du monde, 1896*," we see that the crew of the ship lived 812 days in a temperature alternating between 40° and 50° below zero. Other travelers reported similar facts. Adults are able to stand cold provided they are not under the influence of alcohol, because alcohol causes a dilatation of the capillaries and thus facilitates the deleterious effect of cold. *Children* are less apt to resist low temperature than adults, because they produce less heat. Excessive mental and physical work and inanition are also causes of death from cold. It is interesting to note that insane individuals possess remarkable resistance power; they never complain of cold.

At autopsy the muscular tissue is found red; the blood is dark; the heart and bloodvessels are filled with blood; ecchymoses are found on the pleura; the lungs are either anæmic or congested. The brain is either anæmic or congested. Wichniewski¹ was the first to observe small hemorrhages in the mucous membrane of the stomach. Since then this sign has been considered pathognomonic. Schrimpton observed an inflammation of the gastro-intestinal tract in soldiers who died from cold during campaigns.

The mechanism of death is as yet not satisfactorily explained. According to Magendie, there is a contraction of the peripheral capillaries, with this result, that there is an increase of intravascular tension; congestion of lungs and brain follows. Pouchet thinks that the blood becomes frozen and stagnant in the peripheral bloodvessels, and this leads to embolism in central bloodvessels. According to Horwatt, weaknesses of the muscular system and of the heart are the main factors in the causation of death.

¹ *Mess. de l'hyg. publ. et méd., lég.* 1895.

PART III.

DISEASES DUE TO CHEMICAL AGENTS.

BY DAVID L. EDSALL, M.D.

As is indicated in the title, the following discussions will be devoted solely to the *diseases* produced by certain important chemical substances. Acute poisonings, belonging exclusively to special works dealing with toxicology, will not be touched upon except in so far as they produce peculiar disease-pictures (such as that in acute phosphorus poisoning), or are of immediate importance in relation to subsequent symptoms. Many inorganic chemical substances which have been accused of causing disease, but apparently do not produce any definite symptoms, have been excluded; while zinc and copper, for example, concerning which there is much difference of opinion, have been briefly mentioned.

Unfortunately, in America the study of dangerous industries must as yet be carried out almost solely through individual effort. The states have only general regulations governing their industries, except in so far as they involve danger of accident or are likely to become public nuisances, specific regulations protecting the workmen from the dangers peculiar to special trades being almost entirely wanting. Governmental study of the influence of trade upon health has been extremely fragmentary, and, from a scientific standpoint, usually extremely casual, so far as the writer has determined by somewhat diligent inquiry among the federal and State labor bureaus and the health boards, though Massachusetts is now undertaking an investigation of this sort that bids fair to be of some breadth. Extensive governmental study of the question, with a view to exercising reasonable control, is very much to be desired in this country, because there are special circumstances which render some European statistics and laws of doubtful applicability here. Among these circumstances are concentration of capital and ownership, the very general use of mechanical apparatus in place of men, peculiarities of the purchasing public, and of the American as compared with the European workman. All these have an influence upon occupation-diseases, and in some instances this is extremely marked.

CHAPTER V.

CHRONIC LEAD POISONING.

In clinical and economical importance, as well as in historical interest, chronic saturnism largely overshadows all other chronic intoxications except that due to alcohol.

Historical.—Evidence that lead poisoning was known appears even in the works of some of the earlier Greek, Roman, and Arabian authors. Their earliest observations relate largely to the medicinal use of lead, accidental and industrial chronic poisoning having been apparently but indefinitely recognized or studied at that time. Ramazzani makes an attempt to demonstrate that Hippocrates had a fairly clear idea of the occupational dangers to workers in metals, but the original scarcely indicates this. Ramazzani seems somewhat over-enthusiastic also in his suggestion that the early death of Raphael was largely due to the use of metallic pigments. Tanquerel states, however, that Nicander knew that lead may cause colic and paralysis, and that Dioscorides saw the dangers to workers in lead and some of the clinical results, and even described certain hygienic measures to prevent them. Galen and some other lay and medical writers of the same general period recognized the dangers from drinking water conducted through lead pipes. The additions to the subject then and later were but fragmentary, however, up to the time of Avicenna, who gave a clear description of lead colic. After this, little that was new was added during the middle ages; but Citois, in 1616, though he failed to recognize the cause, aroused widespread interest in epidemic colic through his description of the conditions resulting from wine drinking by the people about Poitou. The name *colica pictorum* was derived from this source, and was soon applied to the colic of painters and of others who worked in lead, since this presented symptoms identical with those seen in Poitou colic. Evidence that the colic due to wine was lead colic was furnished by Wepfer, in 1671; and Sir George Baker demonstrated the same thing a century later in regard to the Devonshire epidemics, which were ascribed to cider. That the danger from this source was recognized much earlier than this is shown by the fact that imperial ordinances were issued in Europe forbidding the use of lead in wine even as early as the first half of the fifteenth century. After Stockhausen showed the frequency of lead colic in the lead miners at Goslar, in 1656, and its dependence upon their occupation, lead poisoning was frequently discussed by medical writers of the seventeenth and eighteenth centuries, one point of some interest being that de Haen appears to have described saturnine gout, though our clinical knowledge of this condition is, of course, essentially due to the initiative of Garrod. Among later writers, two stand out with especial prominence, one of them being supreme. Tanquereldes Planches, in 1838, published the result of a ten

years' study, including 1,217 cases, which is by far the most profound and important work ever devoted to the subject. His countryman, Duchenne, first studied thoroughly by modern methods the nervous disorders produced by lead.

From the economist's standpoint it is noteworthy that no chemical so readily capable, in its ordinary uses, of causing chronic poisoning, is handled by such large numbers of persons, and none is employed for such manifold and important purposes. Layet¹ made a list of 111 occupations in which industrial lead poisoning may more or less readily occur, and my reading and clinical experience have added a considerable number of others in which poisoning has actually been observed. The influence that may be exerted upon the productiveness of persons engaged in some of these occupations is illustrated by the statement of Kaup,² that the statistics of the sick benefit societies of Vienna show that among the printers and type founders the cases of definite lead poisoning throughout a period of ten years numbered more than the cases of tuberculosis; and, besides many disturbances of health that were essentially due to lead were probably grouped under other headings. Yet these persons exhibit tuberculosis more frequently than the general populace. The printers, painters, potters, and earthenware makers, in and about Vienna, numbering in all about 44,380, furnish yearly at least 1,563 cases of lead poisoning, with 43,045 sick days from this cause alone; and in the whole of Austria there were in this small group of workers about double this number of lead poisonings yearly, with the result that these persons were pure consumers instead of producers for from 85,000 to 90,000 days yearly. These figures are worse than those from some other sources, and the conditions in Austria are undoubtedly bad as compared with those in a number of other countries; but these statistics are given because the manner in which they were gathered is, on the other hand, exceptionally satisfactory for this purpose, and, while they would be somewhat misleading if applied to the world at large, they indicate conditions that may actually exist in other countries where occupations are not specifically controlled by law. They serve to demonstrate the importance that these and some other occupations may have for the economist, and for the clinician as well.

The clinical interest in the subject is even wider and more complex than the economic, for many of these industries furnish products that occasionally cause poisoning in those who use them, as well as in those who make them; and lead is, furthermore, used in many other ways that involve little or no risk to the producer but occasionally endanger the consuming public. Accidental lead poisoning is much less important than industrial, and is less common now than it was a decade or two ago; but its sources are almost innumerable, some of them being evident, some most unexpected, and not a few dependent upon the use of lead in preparations which are of secret nature and therefore more dangerous because the risk from them is often discovered only through the occurrence of poisoning. The clinical importance of the subject and its complexity are also very largely increased by the fact that saturnism at times appears in

¹ *Poisons Industrielles.*

² *Gesundheitsgefährliche Industrien*, etc., 1903; edited by Bauer; pub. by Fischer, Jena.

most peculiar clinical guises, and the nature of the condition is extremely likely to be overlooked, particularly if a source of intoxication is not readily suggested by the history.

Etiology—Race.—Racial susceptibility is not usually recognized, but Mr. J. T. Monell, of Flat River, Missouri, whose experience as an engineer in lead mines is probably unexcelled, and who has observed lead poisoning accurately, states that he is convinced that negroes have an undoubted tendency to lead convulsions; a statement which is very suggestive in regard to the general question of race, and which agrees with the general neurotic history of the negro. Investigation of this point in the records in some of the Philadelphia hospitals shows extremely few cases in negroes, since very few are employed here in occupations that cause exposure to lead. Of the 6 cases of which records were found, 3 were encephalopathies.

A point that is not wholly pertinent under this heading, but that is of importance, is that, in this country, a very abnormal percentage of cases occurs in foreigners, which may be chiefly attributed to their exposing themselves unduly, owing to imperfect understanding of the English language and to their personal habits.

It is of interest to note that some of the lower forms of life seem to be more or less immune to the action of lead, and that the higher types of animals also differ greatly in their susceptibility. In the latter, it is probably largely a question of the facility with which they make soluble, and absorb, the more insoluble forms of lead. For example, Mr. Monell states that he has observed that dogs and cats live but a short time about the mine where he is at present, while the cows in the neighborhood come regularly to drink the turbid water below the place where the ore is washed, and, although the sediment from this water contains as much as 3 per cent. of lead sulphide, the cows show no alterations of health. Similar observations have been made before. The explanation probably is that herbivora have a relatively small amount of hydrochloric acid in their stomach contents, while carnivora have a relatively large amount; the latter, therefore, can get much larger amounts of insoluble lead salts into solution as chloride.

Heredity.—Fairly good support for the reasonable proposition that there is a family tendency to lead poisoning is given by various observations, such as that of Oliver, in which a father and four sons had fatal saturnism. Though habits and environment may often have had an important influence in such instances, the latter factors are probably better excluded in the reports of intense involvement of certain families in some water epidemics. Anker alone has described a case of direct heredity producing lead paralysis; but this case may be excluded, as it developed only when the child was several years old, and the father, not the mother, had plumbism. The observations of Porak and Oliver that foetuses of animals poisoned with lead have the metal in their tissues, and particularly the careful study of Legrand and Winter, which showed relatively large amounts in the organs of a premature sickly infant that died a few days after birth, and that was born of a mother chronically intoxicated with lead, indicate strongly that the frail infants of lead-poisoned mothers, that are so likely to die soon and usually of convulsions, have often acquired saturnism directly from the mother.

Age.—The argument of Russell for the greater predisposition of those past middle-life is not wholly convincing; but that of Geo. H. Wood,¹ is. It is generally agreed that children, when employed in trades that expose to lead, are especially likely to suffer, though this may be partly due to greater carelessness, and partly a question of relative dosage; a child weighing fifty pounds would be more likely to suffer, if equally exposed, than an adult weighing three times as much. Brown, Putnam, Sinkler and others consider, indeed, that children have a relative immunity, their most effective argument being that in the epidemic in the family of Louis Philippe, at Claremont and in Brown's water epidemic at Tredegar, children were largely spared. Equally impressive testimony for the contrary view is found in the occasional observation of the poisoning of a number of children in a family from causes that affected the adults but little, if at all, such as Baines' fatal cases due to burning staves from barrels that had contained white lead—though here again relative dosage may play a part. But most important indications of a special susceptibility of children are seen in the recent reports of Turner and Gibson² of wholesale poisoning in the Queensland children. A definite answer to the question whether there is a special susceptibility in childhood is, however, of interest, but not of great practical importance; for the essential facts are, that children are less frequently exposed to accidental poisoning, and far less commonly to industrial poisoning; but when exposed they often suffer.

Sex.—Oliver³ particularly insists that women show a strong susceptibility to lead poisoning, and many authors agree with him. It is unquestionable that, if equally taxed physically and equally exposed to lead, women suffer more than men; but there is no satisfactory evidence that they exhibit any special susceptibility that is dependent upon sex as against general physical resistance. Lead poisoning in women is of relatively little consequence in this country; in the past five years ninety-eight industrial cases in men have been admitted to the wards of the Episcopal Hospital, Philadelphia, while there have been no industrial cases in women. This is sufficient evidence of the recognized fact that women are but little exposed to industrial lead poisoning in this country, for this hospital draws from a large number of such industries. In a few occupations, such as decorating pottery, women are freely employed here, and are then much exposed unless carefully protected.

Period of the Year.—Both industrial and accidental poisonings are influenced by this factor. It is generally recognized that workers in lead suffer more frequently during hot months, possibly because they take in more fluid and thus wash down more lead into their stomachs, (increase in the use of alcoholic beverages perhaps also playing a part); probably, also, because the more actively functioning skin absorbs lead with relative readiness. The especial frequency during the summer and autumn of accidental cases due to drinking-water has been repeatedly noted, particularly in the more recent English epidemics, and has been shown by the extensive work of Power and Houghton⁴ to be apparently due to

¹ *Gesundheitsgefährliche Industrien.*

² *Australasian Medical Gazette*, 1897, 1899, 1904.

³ *Dangerous Trades.*

⁴ *Reports of the Medical Officer of the Local Government Board of Great Britain*; for 1895, 1900-01, and 1902-03; *Supplements.*

the tendency of waters coming from peaty gathering grounds to be especially acid at these periods of the year. The acidity seems to be due chiefly to organic acids produced by bacterial decomposition of vegetable matter in the soil.

Previous Diseases and Previous Attacks of Saturnism.—Any preëxisting disease that reduces the resistance, perhaps chronic renal trouble especially, increases the liability to attack. The tendency to further attacks, after once suffering from saturnism, is very striking. This is usually due to further exposure, but Bernhard especially has dwelt upon the fact that characteristic symptoms may appear without any renewal of exposure, one case having shown a new appearance of paralysis twenty years after exposure had ceased. In the last-mentioned instance there must be doubt whether the later attack was due to the renewed presence of circulating lead; but in some less-protracted cases this was almost certainly the cause. Such instances are apparently due to the escape into the circulation of previously insoluble deposits of lead. Kauffman considers that deprivation of food is often responsible for this, through breaking down of tissue in the process of emaciation and the consequent setting free of tissue combinations of lead; but it is quite as likely that this is due to reduction of general resistance.

Habits.—Alcoholism is unquestionably very important in increasing the liability to saturnism, and alcoholic excess frequently determines the actual onset of an attack, particularly of encephalopathy. Maximilian Sternberg's theoretical views to the contrary are opposed to an almost unanimous clinical opinion, and to the experiments of Combemale, Francois, and Oliver. Sexual excesses are especially insisted upon by Oliver as a predisposing factor, women of loose life suffering particularly. All other depressing excesses, lack of exercise, and unhygienic habits, strongly favor poisoning; but the most important factor of all in a vast proportion of industrial cases is carelessness as to cleanliness. In most industrial poisonings, and therefore in the majority of all instances, the lead is actually ingested as a direct result of eating, drinking, using tobacco, and the like, without properly cleansing the hands, and often in lead-laden rooms; or lead is taken in through skin absorption, largely as a result of lack of cleanliness of the clothes or person. There is a tradition among some workmen that tobacco chewing is a prophylactic, a mistaken idea in general, though it might possibly act occasionally as a crude but unhygienic preventive if accompanied by industrious spitting.

Occupation.—This is overwhelmingly more important than any other factor and the occupations in which lead poisoning may occur are manifold. Some are naturally much more dangerous than others, the worst being those in which lead is freely handled and in which the exposure is most continuous, and particularly those in which there is much lead dust. Bauer mentions the following as the most dangerous: lead mining and smelting; zinc smelting; working in white lead and lead colors; making lead pipes and various other lead objects; making pottery and earthenware; type setting and type making; working in electric-storage-battery factories; file making; diamond cutting, and polishing gems and semi-precious stones; weaving, especially Jacquard weaving; making tinware; and installing gas and water pipes. Of these, file making and Jacquard weaving may be practically excluded in this country, because of improved

methods; type setting seems certainly to produce saturnism only rarely here, because of improvements in the type and mechanical methods have largely supplanted handwork; and apparently tinsmithing is not particularly dangerous at present, owing to improvements in solder and in general hygienic conditions. Installing gas and water pipes is certainly not a common cause, but it may evidently be more dangerous if in large operations men are exposed more or less continuously to the dangerous parts of the work, for an epidemic occurred recently in Vienna in the men who installed the pipes for the new water works (Kaup). Diamond cutters, who have their diamond chips set in lead staffs, are said by Norden, of Amsterdam, to show saturnism in nearly every instance, if they have been long at this work; but Pel, who also is in the centre of this industry, says that plumbism is uncommon among them. In this country, diamond cutting, which is confined almost entirely to New York City, Brooklyn, Cincinnati, and Boston, has aroused no interest in relation to lead poisoning; and lapidaries here, as well as others who once used lead wheels in grinding (cutlers, razor-grinders, etc.), appear to be now very little exposed to lead, chiefly because of the increasing substitution of carborundum wheels. In the whole country, diamond cutters and lapidaries together number, at any rate, only a few hundreds. Razor grinders and cutlers are said to have still a somewhat dangerous custom of rubbing lead on the surfaces of their wheels. The other occupations mentioned by Bauer are all dangerous here. Poisoning in miners occurs principally in carbonate mines, and not in those in which chiefly the sulphide is present, a fact that is usually considered to be due to the insolubility of the sulphide. Mr. Monell, however, considers this to be at least partly due to the fact that carbonate mines are likely to be dry, and therefore more dust is produced in them, while sulphide mines are often wet; and the water in the latter usually contains sulphuric acid, which prevents formation of the carbonate from the sulphide. A process recently introduced into several places in this country, of separating the lead in the comminuted ore by means of a blast of air, in order to overcome difficulties previously met in washing some ores, seems likely to be very productive of plumbism through the dust created. Smelting ores containing lead is dangerous, particularly when the ventilating apparatus is not excellent. There is doubt whether this is due purely to inhaling or swallowing solid particles, or partly to inhaling lead vapor; but it is extremely probable that the latter is of little or no consequence, for (Leclerc de Pulligny) at the volatilizing temperature of lead, gases are irrespirable; and Lodin also found that at temperatures between 250° and 300° C., no lead was volatilized, although this is far above its melting point. Nevertheless, the heat produced in smelting undoubtedly adds to the danger by increasing the motion of the atmosphere and hence the intake of lead dust.

Of all occupations the manufacture of white lead and of lead colors furnishes the greatest proportion of cases; though electric storage battery makers, and, in potteries, those engaged in dipping the ware into the glaze and handling it immediately afterward, in spraying decorative glazes, and in dusting on pigment in the decalcomania process, are in practically as much danger as lead workers, unless cleanliness is insisted upon and hygienic improvements such as exhaust fans, proper fritting of the glaze, etc., are used. The possible dangers in white lead works are sufficiently

shown without further discussion, by Kaup's figures for the Bleiberg Leadworkers' Union in Klagenfurt. In 1894, the 45 members showed 61 attacks of lead poisoning (135.6 per 100), and the average per man was 46.7 sick-days in the year. Since then the conditions have fluctuated and in general have improved, but the attacks in a year have never fallen below 56.4 per 100 men. In Herbert's works, in the same town, the attacks each year, per 100 workers, have ranged from 13.2 to 24.6. The influence that has apparently been exerted by careful regulation of this industry in France is seen in the statement of Leclerc de Pulligny that although Paris and Lille are the centres for the production of white lead in France, the cases of lead poisoning in the hospitals of Paris among those employed in this occupation numbered only 13 in two years. Electric storage battery factories, though not numerous, are very dangerous, unless they are well conducted. At the Episcopal Hospital in Philadelphia there were 23 cases in the wards in a little over two years from one factory, and many others in the out-patient department; since this time they have been going chiefly to a new hospital nearer by. The "lead burning" in this industry has an especially evil name among the workmen; but, as already noted, it is not probable that lead vapors are respired, and most of the patients had done no lead burning themselves. A large proportion of them, as is so commonly the case in any industrial lead poisoning, were unskilled laborers. Most of the trouble could be overcome by exhaust fans, hoods, and scrupulous cleanliness of the rooms and the men. Concerning potteries, Prof. Edward Orton, Jr., of Columbus, Ohio, who has been the pioneer in America in putting the teaching of ceramics on a broad basis and who has extensive knowledge of the conditions throughout the country, states that there has been much improvement, particularly in the use of exhaust fans, etc.; but proper fritting and some other important measures are still little used. The dusting and spraying processes are, unless controlled, exceedingly dangerous, and in one pottery it is customary to employ frequently in this work persons with tuberculosis, carcinoma, or other diseases, because none who hoped to live would accept the risk, even at high wages. The measures that are frequently used now to protect these persons are not effectual with the dippers and their helpers, who have their hands almost constantly covered with lead glaze. Proper fritting of the glaze is, however, an almost complete preventive.

Painters are common sufferers, and usually in inverse proportion to their cleanliness, intelligence, and skill. For example, a large proportion of those affected had been merely acting as "helpers," while out of their usual work, and were not painters by trade. A considerable number of the skilled artisans, however, always suffer; burning off paint, through the dust produced, polishing painted surfaces, particularly when this is done by hand, and to some extent perhaps inhalation of lead laden turpentine vapor in interior painting, all make them more or less unavoidably liable to intoxication, though, as is always the case, lack of proper cleanliness is the chief factor. The difficulties in controlling poisoning in painters have led to the passing of laws in France and Belgium forbidding the use of lead paints in public buildings, and the new French law forbidding the use of lead paints in any buildings is, as stated in a letter from the French Bureau of Labor, likely to be in force soon, as at the

time of writing it was before the Senate, having passed the Chamber of Deputies.

Among others in some danger are the makers of rubber goods, particularly the heavier kinds, and of glazed and enameled metal ware; glaziers, ship builders, sailors, laborers in structural iron works (handling freshly painted iron), Bessemer steel workers (Ormerod), workers in brass foundries and occasionally in other foundries, makers of the modern "secession" brie-a-brac, etc.; lace and passementerie makers, and workers in silk mills (when the silks are weighted with lead).¹ The great number of textile workers makes the determination of the conditions existing in their occupations of extreme importance. Poisoning among them from lead dyes was once rather common; trades people and trade journals tell me, however, that lead chromate is still used a little, but this is now of insignificant importance; a statement that is in consonance with the known general use of aniline dyes and also with the experience of the Episcopal Hospital, in Philadelphia, where in the midst of vast textile industries we have had no industrial cases in women in the past five years, and where among the ninety-eight industrial cases in the men's ward in this time there was but a single weaver, and this man was probably poisoned from another source.

In any obscure case the details of the patient's occupation should be investigated most minutely, for occupational sources of lead poisoning are multitudinous and often utterly unexpected.

Accidental Poisoning.—Detailed investigation of many points is often necessary in this instance, also, to determine the source and do away with it. Water is, of course, the most common source, though its frequency has been distinctly lessened by the considerable reduction in the use of lead pipes for public and particularly for private supplies. That lead service pipes are still important in towns is evident, however, for causal conditions in most places have not greatly changed since the epidemic in Sheffield, England, a decade and a half ago, in which six physicians alone saw in six months one hundred and twenty-nine cases; and town epidemics have, in fact, been repeatedly discovered here and in Europe since then, as have house epidemics from private water supplies. Lead tanks for domestic water supplies have gradually disappeared in most places, on land as well as on ship-board, since study of the *colique sèche* of the French navy, and other observations, showed their danger; but that tanks containing lead still have opportunity to do extensive harm in some regions is shown by the reports concerning the Queensland children. Drinking-water becomes poisoned in a number of ways. The carbonic acid in rain- or spring-water may be the cause of poisoning, especially when new lead pipes are in use, soluble acid carbonate being formed; a deposit of relatively insoluble basic carbonate is gradually formed on old pipes, and acts as a partial but not absolute protective. Power and Houghton emphasize two especial causes, one of them a direct oxidizing or "erosive" action due to oxygen in solution in the water; the other the formation of soluble salts of nitric, nitrous, or organic acids; and of these, they consider the latter to be of much the greatest importance. Benjamin Franklin referred to the essential points of these latter obser-

¹For recent conditions in Austria concerning this point see Kaup, *loc. cit.* It has not been well studied recently elsewhere.

vations in 1786 in a letter to Benjamin Vaughan, in which he speaks of a family that had for several years drunk with impunity water collected from a leaden roof, until young trees grew up and their falling leaves were deposited on the roof; these then decomposed and "lent to the water its baneful qualities and particles" and produced a series of cases of poisoning in the family. This occurrence is probably the same as that described by Tronchin and referred to by Oliver.

Lockhart Gibson makes an interesting suggestion concerning the possible poisoning of the Queensland children by ingestion of lead from painted wood work of houses; he found appreciable quantities of lead in the dust collected in rooms and also on the hands after they had been rubbed over painted surfaces, especially if the hands were moist. Sleeping in freshly painted rooms has occasionally been the cause, the lead in this instance being inhaled and apparently carried by the turpentine vapors. Poisoning of women, practically epidemic in its extent, has been observed from washing the clothes of lead workers, a fact that suggests the possibility of occasional poisoning in the wives and children of lead workers, from careless habits as to clothing, etc.; the opportunities of the last mentioned kind are shown by the fact that plumbism is said to have arisen in the dogs of lead workers from sleeping on their masters' coats, and human cases due to sleeping on horsehair sofas have been reported (horsehair as well as bristles of brushes and some other articles being dyed black with lead sulphide, and the manufacture of these articles having occasionally produced industrial poisoning). Glazed earthenware and enameled metallic vessels that are used for cooking and preserving foods, have caused poisoning, though this is uncommon now, and extremely so with the better grades. The lead in the solder or tin itself at one time made the eating of canned goods, or the use of tin vessels for acid foods, somewhat dangerous, but the risk is now minimal owing to improvements in the tin, the solder, and the methods of sealing; and the actual number of cases known to have been poisoned in this way, even in earlier years, is small. Because of its cheapness, lead is, however, sometimes used in sophisticating tin and other drinking vessels, a point of interest chiefly in relation to children. Variot has recently reported saturnism in a child from this cause. The now nearly obsolete custom of making drinking and other vessels of lead caused many cases in earlier times, especially when such vessels were used for cider, wine, or other acid beverages. Children's toys, when made of lead, have caused poisoning in recent times (Variot), and the same may occur when they are colored with lead pigments, though the latter are now probably used but little for this purpose. Candies were at one time colored with lead dyes, but this is rare at present; and the use of lead chromate in baker's products has hardly been heard of since Marshall showed how freely it was being practised in Philadelphia, and D. D. Stewart¹ very acutely demonstrated here a most dangerous epidemic from this cause. Foods in general are so carefully watched now that there is little danger from them directly, though epidemics are still occasionally reported in Europe as a result of "filling" mill-stones with lead, the lead being gradually ground off into the flour. The opportunities for such an occurrence in this country have been greatly reduced by the fact that rol-

¹ *Medical News*, December 31, 1887; and *Third Annual Report State Board of Health of Pennsylvania*.

ler mills have practically done away with the old fashioned mill-stones, though where the latter are still used, possibilities of lead poisoning exist in this country, for lead is still used in these mill-stones here. Soda water or carbonated water in siphons may cause poisoning, particularly if the tanks, the siphons, etc., contain lead; and Cao has recently found lead in carbonated water in siphons and reported a series of poisonings due to this cause; but, excepting, perhaps, for some old apparatus, there is little danger from this source in this country, as block tin and zinc have almost completely supplanted lead for this purpose. The siphons tested here were made of tin or zinc. Cosmetics, hair dyes, and false teeth are commonly known to have been sources of poisoning. Medicinal lead poisoning was known to the physicians of the ancients; it is generally thought to be very uncommon now, but Miller¹ has recently reported two personal observations and discussed a series collected from the literature, and he thinks that slight or moderate symptoms from this cause are probably not infrequent. The use of diachylon ointment over large eczematous surfaces is certainly dangerous, and has caused fatal poisoning in infants (Pässler, Hahn); and poisoning from internal use of diachylon as an abortifacient has also been repeatedly observed in recent years in England (Ransom).

Infants have also been poisoned by dusting powders containing lead, or by cosmetics or ointments used on the person of the nurse. As instances of extremely odd sources of accidental poisoning, Dodge's case in which the patient was ultimately discovered to have taken for a month a dozen No. 7 shot before each meal "to cleanse his blood," and Küster's case of a soldier who was wounded in 1870, developed lead poisoning in 1888, and recovered after the partially dissolved fragments of the ball had been removed by operation, may be mentioned. Several fairly authentic cases that appeared to be due to the same cause, though less protracted in their course, are on record.

The duration of exposure before the development of plumbism has naturally varied greatly. This is usually tacitly or openly attributed to variations in individual susceptibility. A certain degree of immunity undoubtedly exists in some persons, others are certainly especially susceptible, and intercurrent factors are known to increase or decrease susceptibility; but it is difficult to establish the importance of immunity in considering industrial cases, because individuals differ so largely in their care in avoiding exposure; and the matter is far from simple in even water epidemics and other accidental poisonings.

Accidental or medicinal ingestion of single large doses has repeatedly caused somewhat prolonged poisoning, usually colic; though encephalopathy has repeatedly, and paralysis has in rare instances, followed a single dose or a few doses. Quensel mentions a case reported by Sommer, in which furor appeared after a few hours' intense industrial exposure; the reference appears to be incorrect, and the report could not be found. Colic and indefinite symptoms of poisoning often occur soon after beginning work in lead. Tanquerel repeatedly saw wrist-drop after a week's exposure, and others have had similar experiences. As a rule marked colic does not occur for several weeks or longer, and symptoms of poisoning

¹ *Therapeutic Gazette*, 1904.

may first appear after even many years of exposure. Paralysis is usually rather a late development, commonly appearing only after preceding cachexia or colic and therefore after prolonged exposure. Encephalopathy is not infrequently seen within a few weeks or months, but often arises late.

Pathology.—The pathology is chiefly not characteristic or obscure; it has not been extensively studied, especially by modern methods. There is usually general emaciation; the teeth and particularly the gums are frequently in bad condition, the latter usually loosened and often slightly ulcerated. The blue line is generally found, particularly in the gums of the central and lateral incisors and the canines, and especially on the lower jaw. This line is due (Fagge, Stewart,¹ Ruge²) to deposits of lead sulphide in the apices of the papillæ, the granules being found partly in the lumen of the capillaries, but more largely in their walls and in the surrounding tissues. The lead sulphide is formed from circulating lead-compounds, through the action of the hydrogen sulphide produced by decomposition of small food particles lying between the teeth and under the edges of the gums. Arteriosclerosis is common in the subjects of saturnism. It is doubtful whether lead produces this directly, experimental work on the subject being inconclusive (Jores); Ruge's observation of proliferative changes of the vessels of the gums in the neighborhood of the lead sulphide deposits is, however, somewhat suggestive in this connection. Lead appears also occasionally to cause chronic sclerotic endocarditis. Pulmonary tuberculosis is very common in lead-workers, and they may show also the ordinary lesions due to working in a dusty atmosphere if their occupation has exposed them much to dust. Chronic gastro-enteritis is common, but no special changes have been described in the digestive tract except pigmentation of the walls of the intestine with lead sulphide, and degeneration of the cells in the ganglia of the intestine; the latter and degenerative changes in the abdominal sympathetic ganglia supposedly produce the attacks of colic. In experimental cases (Oliver) the intestine is often found in extreme spasm; and this is very probably the mechanism of producing the pain in colic. In his experimental work on animals and in his postmortems, Oliver found, as the earliest lesions, intercellular cirrhosis of the liver and an acute nephritis, with degenerative changes in the epithelium of the convoluted tubules; cellular proliferation within the capsules and around the afferent vessels of the glomeruli, and later within the glomeruli themselves; and, finally, progressive interstitial nephritis. A considerable number of other observers have noted nephritis in the early stages and have produced it experimentally. Oliver believes that these hepatic and renal changes occur regularly in lead poisoning and are the chief lesions due directly to lead; many and perhaps most of the other symptoms he considers the result of secondary metabolic disturbances. In old cases interstitial nephritis is a very common lesion, often the most important. In a small proportion of cases the lesions of gout are present. The bones have occasionally shown lesions that have a doubtful relation to lead. Bone-marrow changes were found by Cadwalader. There was marked hyperplasia of the marrow, the granular myelocytes were numerous, and

¹*International Clinics*, vol. iv, Seventh Series.

²*Deutsch. Archiv. f. klin. Med.* Bd., lviii.

many nucleated red cells often collected into characteristic erythroblastic areas were found.

In cases with nervous lesions, the paralyzed muscles are more or less atrophic and show degeneration of the muscle cells and proliferation of the nuclei; Oppenheim has, indeed found marked changes in non-paralyzed muscles. The peripheral nerves whose territory was involved clinically have been many times investigated and always found degenerated, the radial being the most common seat of changes. The alterations are usually parenchymatous, rarely involve the connective tissue severely as a result of lead alone, and are situated chiefly in the peripheral portions of the nerves. Gombault has produced these changes experimentally. The nerve-cells of the anterior horns of the spinal cord usually show no noteworthy changes, though in relatively uncommon instances they are degenerated. Madam Déjérine-Klumpke,¹ and later Spiller,² sifted these down to five or six reliable cases, besides Spiller's own case, in which there were marked alterations. Nissl, Schaffer, Stieglitz, and Rybakoff, produced spinal changes experimentally. Spiller's case, Philippe and Eide's case, and Steiglitz's animals, also showed lesions of the ganglia on the posterior roots. The usual gross cerebral lesions in encephalopathy have been œdema and anæmia, flattening of the convolutions, thickening of the pia, and small hemorrhages. Microscopical studies have been very few. Quensel found marked changes of the cortical cells, and proliferation of the nuclei in the vessel walls and of the glia-cells about the vessels. Similar changes were found by McCarthy³ in dogs, and Spiller also noted in his case proliferation of the endothelial cells on the surface of the pia. Changes have been observed in the cerebrum in cases without encephalopathy; and the changes in the nervous system, in human subjects and various species of animals, are not peculiar to lead poisoning.

Mode of Entrance and Pathogenesis.—As already stated, the usual channels of entrance are ingestion into the stomach, or inhalation of particles into the respiratory tract, followed by solution and absorption in either of these places. Skin absorption certainly plays some part, though just how much is uncertain; it is, indeed, uncertain whether any considerable part is played by inhalation, for ingestion is undoubtedly the most important method. Inhalation of the actual vapor of lead is, as already explained, a very questionable occurrence. The digestion experiments of Oliver, Bedson, and Best, make it appear probable that most of the lead that reaches the tissues is transformed into chloride in the stomach, and absorbed either there or from the upper intestine. Probably a part of it is got into solution in the intestine by means of bile or organic acids. The gastric juice dissolves lead quite freely through the agency of the hydrochloric acid; other elements of the gastric contents play no part, and this action is even much interfered with by the presence of protein, because protein either forms insoluble lead protein compounds or saturates the hydrochloric acid, and thus prevents the forma-

¹ *Des Polynévrites en général et des Paralysies Saturnines en particulier*, Paris, Ballière et cie, 1889.

² *Contributions from the William Pepper Laboratory of Clinical Medicine*, 1903.

³ *Contributions from the William Pepper Laboratory of Clinical Medicine*, 1902.

tion of lead chloride, a fact of considerable importance in prophylaxis, as it shows the rationale of having workers in lead take a full meal or plenty of milk before beginning their work and at mid-day. The bile dissolves lead freely, and acid bacterial-decomposition products in the intestines may also dissolve a considerable quantity. It seems, indeed, probable that more absorption takes place in the intestine than the authors mentioned indicate, for the contents of the small intestine are usually acid throughout. Pancreatic digestion does not increase the solution of lead. The form in which lead reaches the circulation and tissues is not known; it is not as albuminates or peptonates, for these are insoluble. Blum, whose original article was inaccessible to the author, is referred to by Bauer as having found that a part becomes insoluble basic carbonate upon reaching the blood and tissue-fluids, and is precipitated as such,—whence comes, perhaps, much of the frequent prolonged immunity from symptoms when only small amounts are taken. Blum finds part of it in the blood in a peculiar stable solution that is not precipitated by hydrogen sulphide; this apparently “undergoes a reaction with the tissues” and produces the symptoms of poisoning. Evidences that definite combinations with the tissues occur, he finds in his observation that after poisoning with lead salts that are insoluble in ether, ether-soluble lead compounds may be extracted from the brain. It seems probable that if tissue compounds are formed, they are unions of lead with the lipoid elements of the nervous tissues, both because of the affinity of lead for these, and because this is definitely known to be the case with some other poisons affecting nervous tissues (chloroform, chloral, etc.). Blyth, however, found most of the lead in the brain in an ether-insoluble form, and probably in the protein fraction. Except for the widely quoted but somewhat questionable observations of Maier, that the cerebral cortex has a special affinity for lead, there is no other evidence of a direct chemical action of this metal on the tissues.

The greatest amount of lead has been found in the liver, by all observers. Considerable quantities are often found in the kidneys; the brain, cord, nerves, muscles, bones, and other tissues contain various amounts. A number of authors list the various organs in order, according to the amount that they usually contain, commonly placing the brain second to the liver; but such an arrangement is ill-advised, for the order must vary greatly in individual cases. Certainly in many instances the brain contains little or no demonstrable lead, even in encephalopathic cases. In three of these the writer found no lead in portions approximating one-third of a hemisphere. The custom of speaking of a special affinity for lead on the part of the nervous system, particularly the peripheral nerves, is based almost entirely on clinical observation and histological alterations, not on facts. The lesions are not necessarily the result of the direct action of lead.

The manner in which lead acts is in many points a subject purely of speculation and controversy. Colic seems to be due to spasm of the bowel, dependent most probably, but not certainly, upon changes in the intestinal ganglia. The changes in the muscles, together with the peculiar localization of the paralysis and the absence of sensory symptoms, led to the now relinquished hypothesis that the paralysis is due to muscular changes, and also suggested the view, that is still not wholly disproved,

that it is spinal in origin. The usual absence of spinal lesions led the supporters of the spinal hypothesis to the conjecture (Remak, Erb) that it may result from undemonstrable functional changes in the cord; but most observers and investigators now lean to the view that the peripheral changes are primary, and Remak himself grants that the spinal origin cannot be very firmly maintained. The constancy of peripheral changes, and the infrequency of noteworthy changes in the cord, make the peripheral the more probable theory; but if it is correct, there is as yet no explanation of the almost regular escape of certain muscles from the paralysis.

Whether the lead acts directly upon the nerves and other tissues in producing the symptoms, or indirectly through setting up disturbances of metabolism, cannot now be determined. The first view is difficult to disprove and seems rational; but there are certain facts, such as the apparent absence of lead from the brain in some cases of encephalopathy and its presence in other cases, that presented no cerebral symptoms, that make the other view wholly possible. Definite opinions upon this point are at present based on mere speculation.

Disturbances of metabolism do occur, though they have not been extensively studied. Clinical observation demonstrates the common tendency to tissue breakdown and emaciation; and destructive increase of metabolism has been shown to occur at the time of the attacks. Some changes in the phosphates, kreatinin, hippuric acid, and uric acid, which are of questionable and as yet undetermined value, have been recorded. Most of the observations on urea excretion, upon which some authors lay stress, have been practically valueless; and the effect on uric acid excretion is unimportant (Lüthje). A noteworthy fact, and one that may be of much interest in relation to basic degeneration of the red blood cells, is the frequent occurrence of slight grades of haematoporphyrinuria.

Lead is excreted chiefly through the kidneys and may be present in the urine long after the exposure has ceased. It is excreted in the bile in large proportions in animals, and some observations (Mann) indicate that it may be partially excreted in the human faeces. A little excretion occurs through the sweat, but this is of slight importance. It has also been found in mother's milk (Bulland), a fact of interest in relation to the infants of lead poisoned women. Lead has been demonstrated in the parotid glands and saliva. The minimum dose capable of producing poisoning when long continued is not clearly determined. Brouardel considered that 1 mg. daily may suffice.

Symptoms.—The clinical course of plumbism consists, in most instances, of the development of more or less marked but indefinite general symptoms, followed after a variable time, usually at least several weeks often much longer, by the appearance of colic. Less commonly but still frequently, paralysis supervenes; occasionally the graver cerebral manifestations occur, also usually after previous colic. There is, however, no constancy in the course of the symptoms: violent colic may open the scene soon after exposure begins; paralysis may develop very early; and in rare cases, without preceding noteworthy symptoms, coma, or an outburst of convulsions or of more or less dangerous delirium, may be the first recognized evidence of poisoning; and occasionally indefinite ill health without distinctive symptoms lasts for years and ultimately causes death.

usually chiefly from chronic renal disease. Cases of the latter form are rare, however, if histories are searchingly taken. Probably a fair number of subjects get well early without showing characteristic symptoms, because the exposure ceases; lead workers often change their occupation upon the appearance of slight symptoms of ill health.

It is not wholly feasible to classify the signs of actual poisoning under the early and the late symptoms, since no symptoms appear at regular times, and no combinations of symptoms are at all constant. It is, nevertheless, important to recognize that general symptoms are practically always present. In the earliest stages they are, usually, chiefly the symptoms of ill-defined disturbances of the gastro-intestinal tract, or they belong to the indefinite sort that are likely to be termed neurasthenia, the patient then presenting more or less weakness, restlessness, insomnia, headache, and mental depression. Frequently mild or pronounced pains in the limbs and trunk are noteworthy early features. A little later, usually when more distinctive symptoms have become apparent but sometimes without these, an earthy or sallow pallor, often very striking and not well explained by the moderate grade of anæmia usually present, emaciation, and more pronounced weakness appear, producing the so-called lead cachexia. Still later, signs of renal or cardiovascular sclerosis often become conspicuous, if the poisoning has been prolonged and severe; and at times such features develop long after the distinctive evidences of lead poisoning have vanished. Progressive interstitial nephritis is probably the commonest ultimate cause of death, though cardiovascular incompetency or the cerebral results of arteriosclerosis are frequent causes.

At any time during the periods previously noted, the more distinctive characteristics of lead poisoning—colic, paralysis, or cerebral symptoms,—may appear with the general symptoms. Colic almost always develops, and usually soon after the first signs of ill health. Paralysis, when it occurs, commonly comes on after some cachexia has appeared; that is after poisoning has lasted for a considerable period. Encephalopathies may develop early if the poisoning has been severe, but they likewise may occur later.

Two conditions, the blue line on the gums and basic granulation of the erythrocytes, are usually present at all stages of poisoning, and often even when there are no actual symptoms of intoxication. Basic granulation (Grawitz, Moritz, Stengel, White and Pepper, Cadwalader) is indeed, so far as is known, constant during the whole time that lead is present in the system, and it appears even when exposure has been extremely brief; White and Pepper¹ found it after four days' industrial exposure, and even twenty-five hours after a single dose of $7\frac{1}{2}$ grs. (0.5 gm.) of lead acetate. Neither of these signs alone constitutes absolute evidence of clinical saturnism, and basic granulation is found in many other conditions; but both are of extreme importance in suggesting that lead is being absorbed, and are valuable confirmatory facts in the presence of obscure symptoms. The blue line, when characteristic, is certain evidence that lead has been absorbed; while basic granulation is only suggestive, though it is extremely so under circumstances that will be mentioned directly.

¹ *Contributions from the William Pepper Laboratory of Clinical Medicine*, 1901.

The blue line, sometimes called Burton's line, is said (Stillé) to have been noted by Spence in 1805, but his description does not seem to refer to the lead line, and certainly it was first actually studied clinically by Burton in 1834, and practically at the same time by Tanquerel; Gull, Fagge, Stewart, and Ruge have made important observations since then. Clinically it appears, upon hasty observation, to be an irregularly linear, or broader, dark-blue discoloration of the margin of the gum. Closer inspection shows that it is frequently a line's breadth from the edge of the gum, though if the latter is loosened and overhanging or is atrophying, the line is often on the very edge. It may appear stippled even to the naked eye, and a hand-lens shows that it is made up of fine, nearly round dots, which are sometimes discrete, sometimes closely clumped together. At times it consists of a few isolated dots or of a very slight and ill-defined line, especially if the gums and teeth are in good condition. It is not usually continuous from one tooth over the next; the portion of the gum situated between the teeth shows it most commonly, but little separate arches, or partial arches may form over the bases of the individual teeth. It is especially marked about the incisors and canines, and particularly in the lower jaw. The common statement that it is absent if the teeth have been lost, Stewart considered inaccurate; he repeatedly saw it in such persons when the gums were not atrophied. Stewart also insists that in its slight forms it is nearly always present, even when the gums are in good condition. Blue patches are sometimes seen on the inside of the lips and cheeks, but these appear to be usually due to a different cause; *i. e.*, to deposit of lead sulphide from the buccal cavity, in areas that have been more or less denuded by rubbing against accretions of tartar on the teeth opposite to them. The blue line must be carefully distinguished from deposits on the surface of the gum or on the teeth. This is best done by the aid of a lens, noting the situation beneath the surface and the dotted appearance; also, as suggested by Stewart, by pushing a small slip of white paper between the edge of the gum and the teeth, this making the characteristic line more distinct and excluding deposits on the teeth. The similar line produced by silver, though relatively very unusual, may rarely cause confusion; this is less likely with the green line due to copper. If there is uncertainty it may be overcome, if desired, by snipping off a small piece of pigmented gum and observing that the pigment turns white (lead sulphate) in hydrogen peroxide, and grows blue-black again in ammonium sulphide (Grehant, Ruge). The blue line persists throughout exposure, and from three months (Oliver) to a year or more after all symptoms have vanished.

Basic granulation of the erythrocytes gives the appearance of a stippling, with granules that vary in size from fine points to others as large as eosinophile granules; it is evident only after staining, the granulations taking basic stains. They are seen in many different diseases, but it is of great importance to note that in lead poisoning they are constantly present, are usually seen in many erythrocytes, individual cells often show large numbers of them, and the granules are ordinarily of rather large size. The latter conditions are extremely rare, especially in diseases that are likely to be confused with lead poisoning, provided the ordinary stains (thionin-phenique, hematoxylin-eosin) are used. The objects

brought out (Cadwalader¹) by the use of polychrome methylene blue are, in part at least, probably of different nature, and seem to be very commonly observed in large numbers even in normal blood; hence, this stain is not satisfactory for purposes of clinical diagnosis, and it is doubtful, indeed, whether any methylene blue stains are wholly reliable for this purpose (Stengel, White). Hematoxylin-eosin does not bring them out properly unless the staining is prolonged. They apparently persist throughout the whole course of poisoning, and vanish soon after lead disappears from the system (White and Pepper), though this point is one that has not been sufficiently studied.

Together with the basic granulation there is usually some anæmia. Oliver states that he often meets with severe grades; but counts rarely show the red cells below two million, and they are below three million in but few cases. There is some reduction of the hæmoglobin; usually not severe and rather less than is proportionate to the decrease in red cells. Nucleated red cells are frequently present in small numbers, occasionally in considerable numbers (Cadwalader). Gilbert finds eosinophilia common in the earliest stages; but this has not been confirmed, and Dr. Cadwalader states that in 37 differential counts he never saw the eosinophiles above 4 per cent., rarely as high as 2 per cent.; the leukocytes show, indeed, no noteworthy changes. On the whole, the blood shows few alterations excepting the basic granulation and some normoblasts; and in this lies an important contrast with pernicious anæmia, in which disease severe basic degeneration is common.

When actual symptoms of poisoning appear they are both general and local. The general symptoms not referable to any special organs, such as the so-called neurasthenic symptoms and the cachexia, have already been noted. Slight fever (99.5° to 100°) is present in unusual cases, and at times may be somewhat prolonged; this may cause confusion in diagnosis. In somewhat greater detail, the most important local clinical effects are as follows:

Digestive Tract.—Anorexia, unpleasant and often sweet or metallic taste, furred tongue and offensive breath, are frequent even early, and the latter symptom is often extreme in well-developed poisoning and has been insisted upon as important, though it is probably due to the common bad state of the mouth and to the disordered nutrition, rather than to any direct influence of the lead. Nausea and vomiting are very common (Tanquerel, Stewart); and Oliver has especially noted attacks of epigastric pain which may be violent. Constipation is the rule, and is frequently extremely obstinate, especially when colic has developed; occasionally constipation alternates with diarrhœa, and rarely there is persistent diarrhœa. Sailer has noted the absence of hydrochloric acid from the stomach contents in seventeen out of twenty-one cases; Stengel and the writer had observed the same in a few cases. This might lead to confusion with gastric carcinoma, if gastric symptoms and cachexia were present; the discussion of Sailer's paper showed that this had actually occurred in one of the cases, and the same mistake was several times recorded before examination of gastric contents became a customary method of observation. Among rarer disorders of the digestive tract are salivation, severe

¹ *American Journal of the Medical Sciences*, January, 1905.

stomatitis, parotitis (which latter may be due to the lead, but seems chiefly dependent upon infections traveling from ill-kept mouths), and ulcerative colitis. Some authors, on questionable grounds, consider appendicitis especially common in subjects of plumbism.

Colic is the symptom of chief importance referable to the digestive tract. It is, however, not due to disturbed digestion, but apparently to spasm of the bowel of nervous origin. In severe accidental poisoning, colic may appear after a single dose, and occasionally in industrial poisoning within a few days. Usually weeks or months of poisoning and frequently similar periods of indefinite ill health precede it. Generally the patient has been constipated beforehand, often severely so, and commonly forebodings of pain have already been felt when the first attack of actual colic comes on. Severe pain then appears, often in the night, in paroxysms lasting for a few seconds or minutes, in some cases even for hours. The outbreaks of violent pain are separated by intervals which last for similarly variable periods, in which there is comparative comfort; the abdomen is often tender in the interval, and dull pain frequently persists, and is sometimes nearly continuous, but violent paroxysms of pain do not often continue for many hours without prolonged remission. The severity of the pain varies a good deal; when it is extremely marked, the patient is in restless agony, or is almost collapsed from suffering, with a weak, small pulse; while in milder cases the pain is extreme but bearable, the pulse small and of high tension, probably from reflex stimulation. The quality of the pain in severe colic seems to be well described by the centuries-old German name, *Hüttenkätze*, given to it, it is said, by the miners and smelters because they believed the wildcats of the mines were tearing out their entrails. It is usually situated chiefly about the umbilicus, but may be diffused over the abdomen; in rare instances it is focalized in such a way as to resemble somewhat closely renal or hepatic colic. The abdominal walls are usually hard and retracted during the paroxysm, and pressure upon them ordinarily gives relief, though in a minority of instances these statements may be reversed. Vomiting is common during the paroxysm, and constipation is usually most obstinate until the spasm of the bowel is over; and it is frequently troublesome long after the pain is wholly past. The secretion of urine is much reduced; occasionally, it is said, it may be suspended for many hours. The duration of an attack, with the paroxysms and remissions, is sometimes a few hours only, more commonly several days, frequently ten days or a fortnight. The severity, however, usually decreases continuously after the first day or two of treatment. Recurrences are the rule if exposure continues. They may, indeed, occasionally develop long after exposure has ceased.

Respiratory Tract.—Aphonia and dyspnoea from laryngeal paralysis are very rare. Asthma is an occasional though uncommon result of the intoxication. Pulmonary tuberculosis is unduly common in subjects of plumbism, partly as a result of inhalation of irritants, partly from reduced general resistance.

Cardiovascular System.—Arteriosclerosis is common in lead workers even at an early age, and, though the point is disputed, it seems to be a result of plumbism. A considerable number of those poisoned for a long time ultimately exhibit the symptoms of cardiovascular incompe-

tency, and die from circulatory failure, or occasionally from cerebral accidents.

Genito-urinary System.—A little albumin, and some casts, are not uncommon in the early stages, especially if the dosage has been large. They are frequently present during an attack of colic. After prolonged poisoning, progressive interstitial nephritis often becomes the most important feature of the case, and it is probably the commonest late cause of death.

Suppression of urine, spasm of the bladder and urethra, and sometimes retention of urine, may be seen with colic. Retention, sometimes with overflow, also incontinence, have several times been observed as persistent symptoms in cases with pronounced nervous lesions of spinal type (J. J. Putnam). Uratic urethritis in a case of saturnine gout, neuralgia of the testicle, epididymitis, and orchitis are rare occurrences, and have a somewhat doubtful relation to lead.

The influence upon the generative organs is seen chiefly in woman. Menstruation becomes disturbed, being usually excessive and irregular; and pregnant women with saturnism are extremely likely to abort or to have premature labors. In the latter the child is often still-born, or it is very frail and usually soon dies. After exposure has ceased, women often pass through repeated normal labors. These facts are of much economic importance in Europe, but are scarcely so in America, where exposure to poisoning is comparatively very rare in women.

Joints and Bones.—Gout occasionally occurs, though the actual relationship to plumbism has been the subject of warm discussion, many maintaining that its occurrence is merely coincidental, many holding it to be causative. The literature seems to indicate that those who see little gout find it uncommon in lead workers; while those who see much gout see it with relative frequency in lead workers. The positive evidence outweighs the negative, but it seems clear that other predisposing causes are necessary in addition to plumbism. Saturnine gout is apparently somewhat peculiar in that it involves joints ordinarily spared; the rapidity, too, with which many joints are attacked is often striking. Gubler's tumor, so-called, is occasionally seen over the back of the wrist or of the metacarpal bones of the hand. It is an ovoid mass due to swelling of the sheath of the tendons, or sometimes of the synovial sac of the wrist-joint, and occurs chiefly in wrist-drop; slight subluxation often exaggerates the so-called tumor. Bone lesions have been described but have a doubtful relation to lead.

Nervous System.—Moderate pain, often indefinitely located, is common in both the extremities and the trunk, especially in early stages. Whether this is due merely to impaired general nutrition, or to essential nerve involvement, is uncertain; but the latter is the probable cause of the actual neuralgic pains, which are not uncommon, and also of the joint pains. These pains in the joints appear in brief or more prolonged paroxysms, which may be very severe, and may last, with intermissions of varying lengths, for days; or they may quickly disappear. They are usually most marked in the knees or ankles. True joint-pains do not seem very common; Tanquerel and others, who have found "arthralgia" common, include under this term all pains in the extremities and even in the trunk. The muscles sometimes ache severely, and may be tender,

especially those that are soon to become paralyzed. Other sensory symptoms are usually slight. There may be paræsthesias, and general sensation may be reduced or lost over the back of the forearm, less commonly over the front of the leg or other localized areas. Hyperalgesia is occasionally noted, and in rare instances there is much tenderness over the nerve trunks. Sometimes actual hysterical symptoms are present, with hemianæsthesia or other characteristic stigmatic local areas of anæsthesia. Cerebral accidents (hemorrhage, etc.) if they occur, may produce hemianæsthesia.

With the diffuse pains, or sometimes in association with colic, and occasionally without other symptoms, certain muscles, particularly those of the calves, may go into mild or severe cramp, which may be very painful. This is not very common in adults, but seems to be so in children (Turner). Gowers and Haenel have observed recurring spasm that closely resembled tetany, and Gowers has seen flexor spasm precede extensor paralysis. Fibrillary twitching of the affected muscles is common after paralysis has developed, and in slight and localized form it is not rare earlier. Buber has described a case in which myokymia of wide distribution was very prominent.

The nervous symptoms so far mentioned, except indefinitely localized pains, are mostly rare or inconspicuous. Indefinite pain is frequent, but more common and more important than any other nervous symptom mentioned is tremor. This is frequently noted, especially in old cases. It affects chiefly the hands, and is usually of slight amplitude and not striking, though it is sometimes coarse and may resemble the tremor of paralysis agitans. It usually increases upon any emotional excitement, and, more markedly, upon effort. Its chief diagnostic importance is in rendering confusion with mercurial poisoning occasionally possible, if paralytic symptoms are absent. Stewart has seen actual paralysis agitans follow lead poisoning, and he also observed curious paroxysmal attacks of severe generalized tremor which he believed were not hysterical.

Most important of all the nervous symptoms, however, and in its ordinary form by all means the most characteristic, is paralysis; and with its usual distribution is of itself almost distinctive of lead poisoning. When typical, it produces so-called "wrist-drop," which is bilateral. There is at first an increasing degree of weakness in the extension of the fingers at the metacarpo-phalangeal joint (paralysis of the extensor communis digitorum), followed by weakness and often complete paralysis of the extensors of the wrist. Palsy often begins in one hand, the other following within a fortnight or less; frequently the hand first involved has been subjected to special strain, or has been especially exposed locally to lead (in lead workers, pottery dippers, etc.), the latter point constituting one of the chief arguments in the questionable claim that lead exerts local effects through the skin. Frequently, in the beginning of the paralysis or later, portions of affected muscles show special involvement; for example, extension of the middle and ring fingers is often noted first, and may long remain most marked. The paralysis is usually subacute in its onset, reaching a marked degree within from a few days to a fortnight; occasionally it progresses very slowly. When well developed, it produces the well-known "wrist-drop," the hand being in flexion at the wrist from paralysis of the extensors, and the fingers moderately flexed owing to

paralysis of their long extensor. At first, the distal phalanges can be extended if the proximal phalanges be first passively extended; for the interossei, the proper extensors of the distal joints, are then uninvolved; the thumb muscles also usually functionate at first. Later, the interossei and the muscles of the thumb are affected; distal extension of the fingers and extension and adduction of the thumb are imperfectly performed, or impossible. The long abductor of the thumb often becomes involved late, but in early stages is usually spared; and the supinator longus is almost never included in the common type of paralysis, a point that is of great importance. The distinctive characteristics of this paralysis are, that it is almost always bilateral, is purely extensor, spares the long supinator and usually the long abductor of the thumb, and there are rarely any sensory symptoms, except, perhaps, limited cutaneous anaesthesia over the backs of the forearms. Atrophy begins soon in the affected muscles, especially those of the back of the forearm; marked reduction or loss of faradic response appears; and the reactions of degeneration develop. As a rule, some of the muscles other than those distinctly paralyzed are weak, and may even show degeneration reactions. The paralysis ordinarily soon reaches the limit of its intensity and extent. Fresh cases quickly improve within a few weeks after proper treatment is started, and generally recover almost completely within a few months if they are not extremely severe. In older cases recovery is slow, and dependent upon the grade of the palsy and its duration; if long neglected and severe, complete recovery is not common, and occasionally very little improvement occurs. Gowers makes two classes of paralysis: in the first, which is the usual one and of good prognosis, the palsy is distinctly primary, atrophy and degeneration reactions follow, and the progress toward more or less complete paralysis, and afterward toward recovery, is rapid; in the second class, which is uncommon, atrophy occurs from the beginning and goes hand in hand with the palsy, faradic and galvanic response decrease together, *pari passu* with the atrophy and the palsy, increase of the palsy is slower, and the prognosis for its recovery is poor.

Forms of paralysis other than characteristic wrist-drop may occur. The Aran-Duchenne type is occasionally seen; in it the small muscles of the hand, the interossei, and the thenar and the hypothenar early become atrophied and more or less paralyzed and these changes produce the "simian" hand. This is not a clearly individualized type in lead poisoning, being usually associated with the previously described form, and simply an exaggeration of some features that are generally present when wrist-drop is at all severe. The Aran-Duchenne form has been particularly noted in persons whose occupation, such as file making, causes a special strain on the small muscles of the hand. The upper arm or Duchenne-Erb type, in which the deltoid, often the biceps and the brachialis anticus, and sometimes the supra- and infraspinati, are involved, occurs occasionally. In it the arms hang by the side, rotated somewhat outward and incapable of abduction, and in severe cases incapable of flexion at the elbow. This form has repeatedly been seen as a separate condition, though it is usually associated with paralysis of the extensors of the fingers and wrist. Contrary to the conditions in the ordinary forearm type, the supinator longus is likely to be involved in this variety. Of

this group of muscles, the deltoid is especially liable to paralysis, and it has repeatedly been the sole muscle palsied; sometimes it has been paralyzed on one side only.

The lower limbs are infrequently affected in adults, and, when they are, the arms usually suffer also; the conditions in children differ markedly in this point, as will be noted later. In the legs, the peronei and the extensor of the toes are the typical seat of paralysis, the tibialis anticus almost always, like the supinator longus in the arm, being spared. In rare instances in adults, more commonly in children, the tibialis anticus is paralyzed, while the muscles usually affected escape. The disease in the legs, as in the arms, is practically always bilateral. The small muscles of the feet occasionally show special involvement; Köster has described an isolated case in which they were affected severely without disease of the leg muscles, and this produced a condition analogous to the "ape-hand" in typical Aran-Duchenne paralysis of the hands. Rarely the disease is situated chiefly in the muscles of the thigh. The knee-jerk may be increased when the legs are affected; it may be normal; sometimes it is reduced or lost.

Paralysis of the cranial nerves is occasionally noted; this is not usually due to isolated neuritis, but is a part of encephalopathic symptoms. In these latter cases, the cause of the paralysis is not certainly known; increased intracranial pressure from congestion or oedema is often present, but direct or secondary toxic effects of the lead on the brain substance are probably more frequently the cause.

The nerve most frequently involved is the optic, though fortunately this is rare; the eye symptoms will be mentioned later. Laryngeal paralysis, which is much more rare (Remak collected only twelve cases), has not been associated with cerebral symptoms in most instances, and, while human pathological studies have not been made, the condition is probably usually a neuritis; this view is supported by studies of horses, which animals were noted by Tanquerel and by many since his time to be especially subject to laryngeal paralysis after prolonged exposure in lead works. The paralysis has most commonly affected the adductors and caused hoarseness or aphonia, though the abductors have repeatedly been paralyzed and produced marked inspiratory dyspnoea. The facial nerve has several times been paralyzed, once (Bury) with the peripheral type of distribution; hence, in this instance there was probably a neuritis. Other cranial nerves that have certainly been separately paralyzed as the result of lead, are the abducens and the oculomotor; and the clinical importance of these nerves has been materially increased recently by the large series of cases in children observed by Lockhart Gibson; paralysis of these nerves, as of the optic, is commonly associated with cerebral signs. Sometimes several ocular and other cranial nerves have been involved coincidentally, usually when other cerebral symptoms were present. Ophthalmoplegia has occurred.

In addition to the localized forms of paralysis, cases are occasionally seen in which generalized paralysis appears, usually advancing from the periphery toward the trunk. In these instances it is probable that both spinal and peripheral changes are frequently present. There are two important varieties, one subacute or acute, the other of slow progress; a third variety is distinguished simply by the presence of fever, with rapidly

extending paralysis. The slow form generally supervenes upon a pre-existing local palsy, usually, of course, of the forearms; but it may be progressive from the beginning. The rapid form is likely to have been preceded by encephalopathy, but this is not always the case. Both ordinarily end in recovery, the acute form often beginning to mend very rapidly within a few weeks or less, the slower form disappearing after more deliberate progress. Very rarely death has occurred from asphyxia. In rare instances, paralysis of the diaphragm has occurred, even without general palsy. A few cases have been seen of diffuse paralysis following the type of progressive muscular atrophy. Some cases have been observed in which conspicuous ataxia, sometimes absent knee-jerks, and only slight paralysis or none, produced some resemblance to locomotor ataxia. Remak states that a definite pseudotabetic form has not been observed; but the reports of Teissier, Raymond, Putnam, Walton, and others, show at least that ataxia may be severe even in the absence of paralysis. There is more doubt in regard to the type resembling spastic spinal palsy, its recognition being based almost entirely upon Putnam's reports, and the diagnosis in these cases was dependent solely upon the discovery of small amounts of lead in the urine. Bechtold, however, has recently reported a rather clear case, and Oppenheim mentions its occurrence.

Cerebral Symptoms.—*Encephalopathy.*—Transitory hemiplegia (Da-Costa) is a rare observation; as is persistent hemiplegia or other cerebral paralysis, except late in the course in old cases when nephritis and arteriosclerosis may cause apoplexy. Aphasia has been noted and choreiform movements have repeatedly been seen, but are rare. There may be hysterical symptoms, with hemianæsthesias and other stigmata, or hysterical outbreaks of excitement or convulsions, especially in predisposed young women.

The most common and striking cerebral symptoms are epileptiform convulsions, delirium, and coma; sometimes a picture more or less closely resembling paretic dementia. In Tanquerel's 1,217 cases, encephalopathy occurred 72 times. Its frequency varies according to the dose, and perhaps according to the nature of the lead compound ingested. In Stewart's chrome-bun series of 64 cases, encephalopathy occurred 15 times. These latter figures are, however, perhaps partly due to the fact that many children were affected. The outbreak often comes suddenly; those who are alcoholic are especially liable, and the author has several times seen cerebral symptoms appear suddenly after slight indulgence in alcohol. Convulsions or delirium usually occur first, convulsions being the more frequent; if coma appears it usually follows delirium or convulsions, particularly the latter. The convulsive attacks are epileptiform with clonic and tonic movements; only one may occur, but, as a rule, the attacks are protracted at varying intervals over days—rarely, even weeks. Epileptiform attacks have occasionally persisted, though this is decidedly unusual, and their relation to plumbism has not been very certain. In the delirious form there is usually active excitement, and the patient may be very violent; convulsions not uncommonly interrupt the delirium, and there are often striking changes from violent intellectual and motor activity to hebetude and quiet. Delusions of persecution, and particularly hallucinations, especially of terrifying character, are common; though they are not confined to such subjects, hallucinations are very frequent

in those who are also alcoholic, and with marked tremor the resemblance to delirium tremens may be very striking. Fever (100° to 101° , occasionally even higher) is not uncommon. The duration may be extremely brief, but more commonly delirium lasts from several days to a fortnight or sometimes longer; in unusual instances the patient remains insane. The fact that delirium may be of sudden and violent onset is at times one of grave moment; one of the patients in the Episcopal Hospital, Philadelphia, who had previously shown very slight symptoms of saturnism (mild colic), aroused the ward suddenly in the night with wild cries of fear, and almost immediately leaped from a third-story window and was killed; a few days later a similar but not fatal accident occurred to one of Dr. Tyson's patients at the University Hospital of Philadelphia. Acute encephalopathies are very dangerous; Tanquerel saw 16 deaths in 72 cases, and as a rule the mortality is put higher than this. Death usually occurs in convulsions, in coma, or from general exhaustion; bronchopneumonia is also quite common.

Symptoms of general paresis have been observed in a considerable number of cases, and it is probable that lead can cause this disorder, though many cases reported under this heading appear to have been other conditions, such as marked exhaustion resulting from acute delirium or from cachexia and marasmus, sometimes a state approaching that in Korsakow's polyneuritis psychosis. When the symptoms resemble general paresis, differences usually exist, in that the onset is very rapid, speech is less disturbed than in ordinary paretic dementia, moral vagaries are less common, and recovery often occurs even from extreme states.

Eye Symptoms.—Disease of the external ocular nerves produces the corresponding muscular paralyses. Nystagmus has been observed. Hemianopsia, usually homonymous, once heteronomous, may appear rarely. Transitory blindness may develop suddenly, usually in encephalopathic cases; this blindness commonly disappears rapidly and completely. Vision may gradually become impaired, with the symptoms common in other forms of amaurosis, and, of these, probably at least one-half show persistent structural changes in the optic nerve (De Schweinitz). Ophthalmoscopically, the transitory cases may show nothing; the changes found in other cases are those common in amaurosis, except that lead subjects show especially marked vascular lesions; and it is also noteworthy that in optic neuritis the lesions are not confined to the parenchyma, as they are in the nerves of the extremities, but are also interstitial and perineuritic. Serious eye symptoms are fortunately rare; De Schweinitz saw only 3 instances in over 15,000 eye cases.

Lead Poisoning in Children.—Plumbism in infancy and early childhood commonly shows such wide clinical divergence from that in adults that a brief separate mention of it is demanded. It is, naturally, not common in the very young, since it is always accidental in them; but it is probably somewhat more common than is usually thought, and, in a considerable proportion of the cases that occur, it is almost certainly not recognized. J. J. Putnam first directed especial attention to its peculiarities, and Newmark, Chapin, Sinkler, Stewart, Brown, Variot, Hahn, and others have added interesting observations, the remarkable reports of Turner and Gibson of its widespread occurrence in Queensland being particularly noteworthy, especially in some of their clinical features.

Symptoms.—It is probable that some of the sickly infants of mothers with plumbism have lead poisoning and die of it. Infants seem, as is to be expected, prone to convulsions when poisoned by lead from this or other sources. Colic is likewise a commonly noted symptom in proved or suspected cases in infants, although in them it alone is, of course, not good evidence of actual poisoning. In older children there is a striking frequency of cerebral symptoms, though colic and paralysis are more important. The spasms of colic may be of the same general character as in adults, but colic alone rarely suggests plumbism in children. The fact, however, that colic occurs repeatedly throughout more or less prolonged periods, and that it may show a lack of dependence upon dietetic error or evident digestive derangement, is suggestive. Turner refers to the marked frequency of pains in the legs, or severe cramps, with colic, these cramps being often the most marked symptoms.

In paralysis in children the legs are almost regularly affected, and usually show the most severe lesions when the arms are included; and a further peculiarity, as compared with adults, is noted by Turner: the peroneal muscles usually affected in adults often escape, while the tibialis anticus is usually paralyzed. There is not a great probability of mistaking these cases for poliomyelitis if they are carefully observed; but the likelihood of considering them diphtheritic or other infectious peripheral palsies, is evident.

Of cerebral symptoms, convulsions have been noted by the largest number of observers, but there is a very suggestive interest in the reports of Gibson and Turner of twenty-four instances in which the chief symptoms were prolonged rigidity of the neck, retraction of the head, and ocular symptoms. Of the latter, paralysis of the abducens and the oculomotor were most frequent, though ophthalmoplegia was repeatedly observed, and blindness was common; sometimes the latter disappeared, and sometimes it became permanent from progressive optic atrophy. These cases were at first reported as chronic basal meningitis; later the regular recovery of general health after removal from the homes or from demonstrated sources of lead, the frequent discovery of a blue line, and of lead in the urine in the cases examined for this, demonstrated that many of them at least were lead poisoning.

The blue line is said by Brown and Turner to be frequently absent. Their evidence is not given in wholly convincing form, and is somewhat opposed to certain other observations; but the lead line appears to be at least less common than in adults.

Diagnosis.—Proper knowledge of the sources of lead poisoning, and alert attention to details in the history indicative of exposure, will often give an immediate suggestion of the nature of the case, even when the symptoms are unusual. Colic and wrist-drop, however, are of course much the most common results, and, when characteristic, are sufficient to bring up the diagnosis at once. Their association with a clear source of poisoning, and especially with a blue line, makes the diagnosis practically certain. The absence of a known source of lead is not of much diagnostic importance, if the other signs are definite; and, even if the blue line is absent (which is unusual), bilateral wrist-drop without involvement of the supinator longus, and with no affection of the flexors and no noteworthy sensory symptoms, is nearly decisive, though to be completely so

it needs confirmation through finding lead in the urine. The search for lead in any case should be undertaken early in the treatment and after giving potassium iodide for a few days. A positive result then does away with the occasional possibility of confusion with the unusual instances of similar palsy due to alcohol or other poisons, or to spinal disease, such as poliomyelitis; a negative result, unless the examination has been carefully and capably carried out, means nothing, even early, and is never of importance late in the case. The slight and fragmentary forms of the blue line, which may require a lens to determine their nature accurately, should be carefully sought when a more characteristic line is absent. Basic granulation that is very marked (with hematoxylin-eosin, or thionin stain), and that is not associated with profound changes of other kinds in the blood cells, is extremely suggestive, and may lead to a correct diagnosis. It is not yet certain whether other metallic poisonings produce basic granulation; Lowenthal had suggestive results with tin, but he considers his experiments of doubtful value; and, too, he used methylene blue staining.

Cerebral cases and the slight or more unusual forms of paralysis are much more likely to be misinterpreted. If they are of industrial origin attention to the nature of the occupation usually suggests the diagnosis quickly, and a search for the blue line and for basic granulation furnishes more direct evidence. It is to be remembered, however, that neither of the latter signs constitutes final evidence that unusual varieties of paralysis are due to lead, and if distinctive symptoms are absent, or a source of poisoning is not known, recourse must always be had to examination of the urine; and in any doubtful case the diagnosis must depend upon this. The chief source of error in the blue line is in the fact that it may persist even for years after lead poisoning has disappeared, and it may, therefore, be present with other conditions that have developed later. When convulsions or eye symptoms are present the possibility of uræmia must be considered. In cases with only general symptoms the finding of lead in the urine is the sole reliable source of diagnosis. In a search for lead in the urine the rougher clinical methods, such as the magnesium-band test, or the observation of a black precipitate of lead sulphide after adding albumin and an alkali and heating, may be tried if desired. If a precipitate is formed and confirmatory tests show it to be lead, this suffices; but these tests are usually negative even when lead is present. The only satisfactory method is to oxidize the organic matter by heating as much as 500 c.c. of urine with one-tenth its amount of hydrochloric acid and two or three grams of potassium chlorate, subsequently driving off the chlorine and concentrating by evaporation. The lead is then recovered by electrolysis, or, as sulphide, by means of hydrogen sulphide.

Prognosis.—General disorders that have not caused serious organic lesions, colic, and the mild and recent palsies, recover entirely under proper treatment. The older and more severe forms of paralysis have a prognosis as to complete recovery that is directly related to their duration and intensity, severe protracted cases rarely getting wholly well. Persistent atrophy and progressive decrease or entire loss of response to electricity are bad signs. Cerebral symptoms are always dangerous, coma being particularly so; if, however, the patient escapes death from encephalopathy, serious consequences rarely follow. Eye symptoms, of

slow onset especially, are of very doubtful prognosis. About half of them have persistent optic atrophy, and this goes on to blindness in a large proportion of cases.

The prognosis as to future attacks depends almost entirely upon the discovery and exclusion of the source of poisoning, renewed outbreaks from old lead deposits in the body being very unusual. If the exposure continues, recurrences are probable and are of worse prognosis than the original attacks.

In renal, cardiovascular, and other changes resulting from lead poisoning, the prognosis is dependent upon the severity and stage of these lesions. If the further absorption of lead is stopped, the progress of the lesions that have resulted is of course slower.

Prophylaxis and Treatment.—Were the industries that cause exposure subjected to reasonable regulations and these actually enforced, and were the workmen not only given opportunity to keep themselves clean, but required to do so, industrial lead poisoning would largely disappear.

Cleanliness is the most important point in prophylaxis, and the most difficult one to carry out, owing to the utter carelessness of most workmen. Much of this is due to a lack of proper comprehension of the dangers and the methods of avoiding them, and many poisonings are avoided in those works where the policy of instruction is adopted instead of the narrow custom of belittling the danger. But many workmen will not voluntarily keep properly clean, and hence those at all seriously exposed should be required to do so. The effect of such regulations is seen, for example, in one large plant, in which lead poisoning at one time even greatly endangered the success of the industry, but in which the workmen are now provided with attractive facilities for cleanliness as to person and clothes, are required to use these facilities under penalty of discharge, and are *given full pay* for the time consumed in daily bathing, etc. Lead poisoning has now nearly disappeared from this plant. Most of the details of the hygiene of construction and operation of plants in this country are dependent upon the wisdom and philanthropy of the operator; they should be controlled by law. The regulations existing in a number of European countries¹ are examples of what needs to be done; the most important of these regulations are those that demand certain forms of ventilation, height of ceiling, isolation of the most dangerous parts of the work from the other portions of the plant, apparatus for the exclusion of dust or for the removal of that which escapes into the atmosphere, daily cleansing, and such construction of the walls and floors as to permit of easy and thorough cleaning, the provision of separate eating-rooms and of free baths, the exclusion of women and children from the dangerous parts of the work, limitation of the hours of work and of continuous exposure of the same individuals to the most dangerous parts of the work, and the services of a physician who has power to "lay off" any suspicious cases from work and who must report such cases. In some countries it is also required of the workmen that they change their clothes and bathe after working, wear gloves or rub their hands with grease when at work, and do not eat, drink alcoholic beverages, or smoke or chew tobacco in the

¹ See *Gesundheitsgefährliche Industrien*; Fürgau, *Gifte and Stark Wirkende Arzneimittel*, Berlin, Haering, 1901 (German laws, etc.); *Poisons Industrielles, Dangerous Trades*, ed. by Oliver.

workrooms. The enforcement of these laws is sometimes unfortunately lax. There are in several countries very specific regulations governing the specific dangers in different industries. Simple examples of this are the requirement that lead colors be ground wet, that pottery glaze be properly fritted, etc.; indeed, the English law concerning the latter point is so rigid that Prof. Orton states it is exceedingly difficult to comply with it and continue manufacturing. A more elaborate instance of specific regulations is seen in the fact that in Germany the production of electric storage batteries is governed by twenty-eight regulations, and many of these apply purely to the apparatus, material, and building construction to be used in this particular industry.

Of the simpler preventive measures, proper cleansing is by far the most important. Respirators are of little use because the men usually will not wear them; sulphuric acid lemonade is of some value, though lead sulphate is absorbed to a slight extent. Theoretically proper, and practically very valuable, is the free use of protein food before beginning work or at mid-day; milk is provided free in a considerable number of plants, and in several it has gained the reputation, which is too favorable, of being an almost certain preventive. Fats, such as olive oil, also seem to have some preventive action; one plant in Philadelphia has long required the men to take olive oil before beginning work and at the mid-day meal, and excellent results are claimed from this. Exercise in the open air, by increasing eliminative functions and general resistance, has a most important influence; companies owning their workmen's houses have repeatedly built them at a distance in order to necessitate a daily walk to and fro, and with very useful results.

When poisoning has developed, exclusion of the source is the first imperative necessity. In industrial cases this means of course, a change of occupation, or, if necessary, cessation of work; in accidental poisoning it often means painstaking and extended search for the source. If the water is at fault lead service pipes should be replaced, if possible. In towns where this often cannot be generally done, the whole supply can be rendered nearly harmless by adding chalk or lime to the reservoirs, or by sand filtration; or the individual may do this himself, or filter the water through charcoal, though these measures are more successful if done before the water passes through the lead pipe. The water should also be allowed to run a long time before any is taken for drinking or cooking purposes, as that which stands in the pipe becomes specially laden with lead.

The active treatment consists in elimination of the lead and of general products of metabolism, and in combating general or local symptoms. The initial action in any case should be to expel any lead present in the gastro-intestinal tract, preferably by means of saline purges; purgatives that act largely through increasing peristalsis should not be used. Purgation is frequently difficult to accomplish, for the constipation is often obstinate if there is colic and sometimes when there is not. In such cases it is often necessary to use large and frequent doses of salines (which may have to be combined with simple enemas, or enemas containing a half ounce or an ounce, 15 to 30 gm., of magnesium sulphate), and to give with the purgatives, to control the intestinal spasm, moderate doses of atropine, pilocarpine or other antispasmodic. Large oil enemas are also

very useful and entirely harmless. In cases with severe colic a movement may sometimes be secured only by giving, before the purgatives, moderate doses of morphine. Control of the constipation is one of the most important features of the treatment of colic, and colic is the commonest symptom demanding treatment. After the bowels are once opened they should be moved at least once (better two or three times) a day until the local symptoms disappear, in order to encourage elimination and prevent return of the spasm. Water should be drunk freely, and if the secretion of urine is low diuretics should be used. After the bowels have been moved, potassium iodide should be given in doses of 5 grains (0.3 gm.) three times daily. If increased beyond this it should be carefully watched, as some observers believe that it may temporarily exaggerate the symptoms by getting more lead into solution. The manner of action of this drug is still a subject of controversy, but it is quite as probable that its influence is indirect, through its alterative effect and through increasing general elimination, as that it acts directly by formation of the soluble double iodide of lead and potassium; the latter action in the body is purely hypothetical. It seems, however, to be in all forms of lead poisoning the best eliminative available. Baths of potassium sulphuret have been recommended by a number of writers; the patient is immersed for twenty minutes in a bath tub containing about six inches depth of water in which six or seven ounces of potassium sulphuret have been dissolved. The pains of lead colic should be controlled by hot applications, or, if severe, by warm baths or hypodermics of atropine or pilocarpine, avoiding morphine unless the pain is so extreme and uncontrollable that it must be used; though it controls the immediate symptoms, morphine interferes with the ultimate purpose of treatment in that it reduces elimination of lead and of general metabolic products through the kidneys, and usually interferes with bowel movements, and, in rare instances, it has brought on dangerous or even fatal cerebral symptoms, probably due to uræmia. Oliver warmly recommends monosulphite of soda in doses of 5 grains (0.3 gm.) for both colic and paralysis in mild cases; my results with it have been unsatisfactory.

Paralysis should be treated by the general principles used in managing peripheral neuritis. Active treatment should be begun only when the acute progress of the palsy has ceased. The most important measures are electricity, carefully graduated massage with passive exercises, and, so far as possible, very slowly increased active exercise. The treatment must be continued for months, and if complete recovery does not occur it should not be stopped until all improvement has ceased for months. Since there is usually decided impairment of the general health in these cases, general treatment is almost as important as local. Moderate general exercise, provided the paralysis permits of it, as it nearly always does, should be used after a preliminary rest in bed; fresh air, sunshine, and a generous diet, must be insisted upon at all times when they can be had. Bitter tonics are useful. Strychnia is not in as good repute as a cure for paralysis as it once was, but is an excellent general tonic and stomachic, and certainly will do no harm if used only after evidences of increase in the paralysis have clearly ceased. The anæmia that is usually present needs, especially, fresh air and food; but small doses of arsenic (100 grain continued for only short periods, as arsenic also causes

nerve-degeneration) will often improve both the anæmia and general nutrition. Iron is not very effectual in such anæmias, and if given should be used sparingly, lest it disturb digestion and increase constipation. The general measures mentioned are likely to be necessary in any case, whether paralysis is present or not, in order to secure recovery of good general health.

Cerebral symptoms need to be managed with much care. There is so much danger of exhaustion that severe eliminative measures should not be used. The bowels must be kept moderately active, and diuresis should be stimulated, especially by free water drinking and by enteroclysis with large amounts (a quart or more) of normal, or preferably half-normal, salt solution at 115° or 120° F. Convulsions or delirium should be treated with large doses of bromides, combined with hyoscine or chloral. Morphine should not be used except as a last resort, and then with care, because of its interfering with elimination. Moderate venesection is a more suitable measure in actively severe cases than is generally taught; there is sufficient evidence of cerebral congestion to justify it in such cases. Good results have several times been obtained from lumbar puncture, and it is possible that it is reasonable to use it if the symptoms are persistent and urgent, but only in such cases.

In both prophylaxis and treatment it is of the greatest importance to exclude alcohol absolutely.

CHAPTER VI.

CHRONIC ARSENIC POISONING.

By DAVID L. EDSALL, M. D.

THE intense general interest in chronic poisoning by arsenic, that was at one time exhibited by the lay public as well as the medical, has well-nigh disappeared; and with good reason, because the opportunities for poisoning are now far less numerous and less obscure. At present, with the exception of arsenical beer, which is of interest chiefly in Great Britain, the occasion for poisoning is given almost solely by a limited number of occupations, by criminal or suicidal use, or by the therapeutic administration of the drug. There are still a small number of articles used by the public in the manufacture of which arsenic is employed in such quantities as to make them somewhat dangerous to those who purchase them; but this is at present of small moment as compared with the past. To the clinician chronic arsenic poisoning remains, nevertheless, and will continue to be, of constant and rather especial interest because, unless somewhat cautious in the use of arsenic, he may see chronic poisoning as a result of his own administration of the drug; he is indeed, much more likely at present to see intoxication from this source than from any other that acts through prolonged ingestion of small quantities, unless he has an unusual situation in regard to occupations that cause exposure. The condition is, however, also of special interest because chronic sequels of acute poisoning occur not infrequently. Most of the chemicals, such as lead, that produce chronic disease, if taken for a long time in small amounts, rarely cause lesions of prolonged or persistent course when only a single large dose or a few such doses are taken. Local effects of direct irritation—gastro-enteritis and the like—may, of course, remain; but the patient otherwise, usually gets entirely well without general disorder, if he escapes such accidents with his life. A few of these chemicals, however, do cause chronic general evil effects as a consequence of acute poisoning, and of this group, arsenic is a prominent member; arsenical neuritis not uncommonly results from a single dose taken by accident or in an attempt at suicide.

Etiology.—Because of the subtle danger to the public at large, more interest has been exhibited in poisoning from various articles in domestic use than from any other source. Wall paper in particular caused many cases of poisoning and excited lively general apprehension. The danger from this source was pointed out by Gmelin, in 1839, but aroused no special interest until Basedow, in 1846, demonstrated its clinical importance; and his observations caused the passing of a Prussian law forbidding the use of arsenic in dyeing paper. It was not until many years later that active attention was given to the subject in this country and

England. Chiefly as a result of the reports of Draper,¹ Wood,² J. J. Putnam, C. P. Putnam, Shattuck and others, so much interest was excited in this country that manufacturers were soon forced into greater caution; but it was only in 1900 that, following the lead of most European countries, a law was passed in Massachusetts strictly limiting the amount of arsenic permissible in papers and articles of dress. This permits only 0.01 grain per square yard in dress-goods, stockings, etc., and 0.1 grain per square yard in papers and fabrics other than dress goods. As a result of this excitement and legislation, the conditions in the country at large have become almost free from danger. Haywood and Warner have made a series of nearly eight hundred quantitative tests of wall paper and in only four did the amount exceed the limit of the Massachusetts state law. Two of these were from England, one of the few European countries that has no laws limiting the amount of arsenic in papers and fabrics; and of five samples that were very close to the limit, four came from abroad. These observations are like those of others; Dr. Charles Harrington states that he and others in Massachusetts, who have examined many hundreds of samples, find regularly less than 1 per cent. that exceed the limit of the state law.

The danger of arsenical poisoning, however, was by no means confined to wall paper; the greatest variety of substances colored with arsenic produced poisoning. It was caused by papers of other kinds, used for wrapping purposes, for making paper flowers, playing cards, and for various other purposes; it was seen as a result of the use of arsenical book covers, crayons, arsenical paint used for interior work, and numerous other objects of diverse kinds, particularly bedroom hangings and clothing of various sorts—stockings, hat bands, gloves, and dress goods of numerous kinds. It is not to be wondered at that the public became excited and apprehensive. There was, and to some extent still is, an impression that green is the chief or only color likely to be arsenical. This is a wholly wrong impression. Red was very commonly arsenical, and various other colors frequently so; in Charles Putnam's remarkable observations of poisoning in infants, the cause was the blue dresses worn by the nurses. The danger from this source also is now slight as compared with the conditions a decade or two ago, but Haywood and Warner found in 1904 that over 11 per cent. of samples of dress goods and over 29 per cent. of stockings contained amounts that were excessive though not highly dangerous. Goods colored red are particularly likely to contain large amounts, though black and green goods often yielded considerable quantities. Another source that is evidently of some importance at present is furs and rugs, which are cured with arsenic; 8 samples of rugs were found to contain over $\frac{1}{2}$ grain of arsenic per square yard, 6 of these contained over 1 grain, and in one the amount exceeded 5 grains, while in one it was just below 17 grains per yard. The greatest danger from furs is local irritant action because of the manner in which they are worn; but general poisoning may, of course, occur.

Foods, in earlier times, were a frequent source of danger, and repeatedly caused both acute and chronic poisoning, arsenic having been used to preserve the color of foods, to keep them from decomposing, and also to

¹ *Report of State Board of Health of Massachusetts*, 1872.

² *Ibid.*, 1884.

provide attractive artificial colors. Large epidemics, such as those at Würzburg, Bremen, Paris, Hyères, and elsewhere, resulted at times, and isolated cases were not uncommon. At present this danger has practically disappeared as foods are now too closely watched.

There are a few other sources of accidental poisoning that are still occasionally active. Acute cases sometimes occur from arsenical fly paper or rat poisons and may have chronic results. Kebler has suggested that chronic poisoning might occur from the use of certain common drugs that are likely to contain small amounts of arsenic as an impurity; sodium sulphate, for instance, may contain appreciable amounts, and this drug is often used daily throughout years. Mr. Haywood states that, in investigating a factory which discharged arsenical fumes, he found that appreciable quantities of arsenic were recoverable from the water of neighboring streams even when collected several miles from the plant; under such circumstances the drinking water might readily be the source of chronic poisoning. The fear that the use of arsenic as an insecticide, more particularly the use of Paris-green against potato bugs, might result in poisoning through eating the potatoes, seems, from the investigations of Kedzie,¹ to be groundless.

Beer drinking has been an extremely important and very disquieting source of poisoning recently in Great Britain, Kelynack and Kirkby² in particular having studied this point extensively. The arsenic was derived from the sulphuric acid used in manufacturing the glucose that is employed in making beer. The conditions in regard to this point have not been investigated in this country, but probably if there is any such danger here, it is very much less than in Great Britain; the sulphuric acid used in the latter country has heretofore been manufactured largely from markedly arsenical iron pyrites while in this country iron pyrites is much less used, and when used it is much less arsenical. Most of the sulphuric acid used in this country is manufactured from brimstone or by the contact method, and is then free from arsenic.

The occupations that cause danger are more limited in number than they were. In those that remain dangerous, poisoning can be very largely prevented by insisting upon proper cleanliness and by instituting measures to control dust, etc. The mines at Deloro, Ontario, for example, have become quite distinguished for the care adopted in protecting the workmen, and for the success obtained. The chief dangerous occupations are the mining and smelting of arsenical compounds and of ores containing considerable quantities of arsenic, among the latter being particularly zinc, silver, and lead. Those engaged in working upon the skins of animals and birds, some hat makers, and dye makers, are also exposed to poisoning. In occupational poisoning, skin symptoms are the most common chronic results.

The chief sources of poisoning, however, are at present suicidal or accidental ingestion of toxic amounts of arsenic, or large or prolonged dosage for therapeutic purposes. This source in particular has been frequently discussed in this country and abroad, and extensive collections of the literature have been made by Imbert-Gourbeyre, Brouardel, and

¹ *Report of State Board of Health of Michigan*, 1875.

² *Arsenical Poisoning in Beer Drinkers*, Ballière, Tindall & Cox, London, 1901.

Marik. Poisoning from therapeutic use of arsenic has usually occurred in cases of skin disease, chorea, pernicious anæmia and other severe anæmias, or Hodgkin's disease, in which conditions the drug is likely to be used for a long time and in large doses. It should be remembered that patients with skin diseases particularly, have many times produced chronic intoxication in themselves by continuing the use of arsenic without the continued advice of a physician, and they should be warned concerning this point.

The practice of eating arsenic for the purpose of increasing the powers of general physical endurance, to stimulate sexual capacity, or to improve the condition of the skin and scalp, has been much discussed in connection with the peasants in Styria in particular; the people of some parts of Hungary, India, and elsewhere have, however, carried out the practice, and, in a lesser degree, it has also been prevalent in some countries among women of higher social station. Doubt was cast upon the existence of the practice by publications that followed v. Tschudi's description of it, but observations by Marik,¹ Friedrich Müller, and others have clearly shown that it was once common in Styria, and was being continued only a few years ago in spite of legal restrictions. It is not so free of bad results as it was once popularly considered to be, Marik and Müller having studied many cases that showed actual chronic poisoning as a consequence.

Pathology.—The lesions produced in chronic poisoning have not been extensively studied; opportunity for investigating them occurs indeed only rarely, as death is an unusual result of chronic poisoning. Even severe symptoms are usually recovered from, more or less completely, and if remnants remain, postmortem observations of them are rarely made until long after the original attack. Skin lesions, anæmia, and changes in the nervous system, are most common. Gastro-enteritis, nephritis, and fatty change of the liver, vascular system, and muscles, are conspicuous in the acute poisoning, but much less so in the chronic form. Of the skin lesions, pigmentation is much the most interesting from the pathological as well as the clinical standpoint. It is due to a deposit, most marked in the lymphatics of the papillæ, of a pigment that is of somewhat uncertain origin; it has not been satisfactorily determined whether or not it is derived from hæmoglobin.

The nervous lesions have been studied by Erlicki, Rybalkin, Henschen and Hildebrand in human subjects, and experimentally by Schaffer and others. The effects are, in the severe cases at any rate, probably exerted on both the peripheral nerves and the spinal cord. In the cord, arsenic produces chiefly degeneration and atrophy of the cells of the anterior horns, sometimes degeneration of the white matter. Schaffer described changes in rabbits that he considered somewhat peculiar to arsenic, but there is nothing distinctive of the lesions as a rule. In human subjects the peripheral nerves suffer most markedly; they show degeneration of the myelin, which is often of segmentary form, and may leave the axis cylinder entirely uninvolved. The latter is, however, often affected, and at times so much so that it can be distinguished only with difficulty.

¹ *Wien. Klin. Woch.*, 1891, Nos. 31-40.

Mode of Entrance and Pathogenesis.—The commonest mode of entrance is therapeutic, suicidal, or accidental administration by the mouth. It has, however, been clearly shown that severe general lesions may be produced by means of external application; this has occurred with arsenical "cancer cures." Arsenic may also be inhaled as dust in some occupations, and the volatile compounds of arsenic are, of course, readily taken in by respiration. Chronic poisoning from wall paper proved to be of much interest in the latter regard. It was by many thought to be due to arsenical dust from the paper, but it was demonstrated by the work of Fleck, Selmi, Hamberg, Sanger, and others, particularly by Gosio, that the view that a volatile compound was formed, is correct. Poisoning from this source was probably due chiefly to this fact. The volatile compound is apparently arseniuretted hydrogen and is produced by a number of moulds, among which *penicillium brevicaulis* is the most important. The energetic capacity of the latter organism to produce this volatile arsenical compound has since been used to a considerable extent as a means of demonstrating the presence of arsenic in organic matter, especially in toxicological work, exceedingly minute amounts thus becoming apparent. The moulds act well at room-temperature and in the presence of oxygen, and their growth is furthered by moisture and by the adhesive paste used in fastening the paper to the wall.

The manner in which arsenic acts on entering the system is a subject chiefly of speculation, but some suggestions that have been made are interesting. In small doses, it seems to stimulate the bone-marrow to blood-formation; in large doses, to produce degeneration of the marrow and cause anæmia. Very large doses set up general tissue destruction. The effect upon the nervous system, as well as some other effects, are thought by certain authors to be due to the formation of arsenic acid from arsenious acid, and to the substitution of the phosphoric acid in lecithin by this arsenic acid. Many of the local effects are due to excretion; this occurs chiefly through the kidneys, but also through the skin and various mucous membranes and glands, such as the liver and the breasts. Mother's milk has caused fatal poisoning of infants. Many instances of disease of the skin, conjunctiva, etc., are due to excretion, though many are due to direct external local action.

Individual susceptibility plays a large part in determining the occurrence of poisoning. Less than a fluid ounce of Fowler's solution taken over a period of a few weeks has caused severe intoxication; while large doses are definitely known to have been taken for therapeutic purposes for even thirty years or longer without ill effects, and arsenic eaters have apparently accustomed themselves to frequent doses of several grains, continued with impunity for very many years. Some animals have considerable natural immunity, and in some birds the immunity is possibly complete. There is still a certain degree of question whether a natural immunity can be increased in animals or man. It has appeared altogether probable that in some instances this does occur, but the work of Cloetta suggests that the apparent immunity is due to lack of absorption of the solid preparations by the mucous membrane. In animals, accustomed to taking large quantities by mouth, subcutaneous injection of amounts ordinarily toxic produced poisoning, so that there seemed to be no real tissue immunity.

Symptoms.—Peripheral neuritis and skin lesions are the most important as well as the most common results. If these are severe they may cause secondary disturbance of the general health. In many instances, indeed, some degree of general disorder develops coincidentally with the local lesions, or before them; but not infrequently marked disease of the skin or nervous system occurs without other noteworthy disturbance of health. If general symptoms are present, they are chiefly anæmia, emaciation, general weakness, irregularity or weakness of the heart action, and vasomotor disturbance. There is also more or less disorder of the gastro-intestinal tract, occasionally evidences of chronic nephritis are present, and exceptionally other symptoms, but one's attention is ordinarily directed chiefly to the skin or the nervous system.

Vasomotor changes are probably the chief cause of one of the frequent and somewhat important skin manifestations; namely, hyperidrosis. This is often very marked and may lead to severe maceration of the skin, especially that of the palms and soles, in which situations hyperidrosis, as is usually the case, is most pronounced. The condition resembling erythromelalgia which was repeatedly seen by Kelynack and Kirkby in beer drinkers, and occasionally by other observers, is probably due chiefly to vasomotor changes, though often associated with arteriosclerosis; in this condition, painful patches of dusky-red or purple color, usually with a well-defined border, appear particularly on the soles and sides of the feet. This condition is often but not always, associated with signs of neuritis. Herpes is an occasional skin-lesion, and is sometimes very severe and refractory; it may occur on the trunk or, at times on the face, extremities, or prepuce. It has frequently been associated with neuritis. Workers in arsenic in particular, sometimes also those poisoned by ingestion of the drug, have a marked tendency to ulcers of the parts especially exposed, particularly those parts subject to attrition; and these ulcers, as a rule, heal very slowly and are often very distressing. Glossiness of the skin is also common.

The most striking skin symptoms are keratosis and pigmentation. Keratosis occurs chiefly on the palms and soles; it may be diffuse, or localized in small areas, and may be of any grade up to the most severe. Ordinarily marked desquamation takes place in connection with the keratosis and this may occur even in large scales or plates. The localized horny areas have some tendency to become epitheliomatous.

Pigmentation is extremely important clinically. It should be watched for when arsenic is being freely administered, as it is both a warning of the possible early appearance of the graver nervous lesions if the drug is continued, and is also itself very disfiguring and at times very distressing to the patient. Furthermore, it has repeatedly been mistaken for other forms of pigmentation, such as that of Addison's disease. It varies in intensity from a slight yellowish-brown tint to a deep brown, and it may be diffused over the whole surface, when it is usually of moderate or slight degree; or, more frequently, it is collected in local areas, particularly on exposed surfaces, or in the folds of the joints, as the axilla, regions exposed to pressure, or in parts, such as the nipples, that are normally pigmented. Sometimes small spots of pigmentation may occur, somewhat resembling moles. The mucous membranes may show pigmentation. Deep pigmentation may be present in local areas, together with a higher degree of

diffuse discoloration. As a rule, the pigment slowly disappears after cessation of the poisoning, but it may remain permanently, to a greater or less degree.

A variety of other lesions of the skin also occur. Erythema has very frequently been seen and it often shows bilateral symmetry; papular, vesicular, and bullous eruptions, pustules, and boils, are common, as are thickening, brittleness, and roughness of the nails, loss of hair, occasionally urticarial, psoriasis-like, and other eruptions.

Among the manifestations suggestive in diagnosis is the condition of the exterior of the eyes. There is often puffiness of the eyelids; the conjunctiva is congested and frequently somewhat swollen; there may be marked chemosis, and there is often marked running from the eyes. These eye symptoms have been particularly noted in the cases due to external action of the arsenic or to drinking arsenical beer; alcohol is probably an associated factor in the latter instances.

Of the symptoms referable to the nervous system, paralysis is much the most important, though a considerable variety may be met. These symptoms are nearly always the result of internal use of arsenic. Paralysis following a large toxic dose usually appears a week or ten days, or even more, after the poisoning, when the acute symptoms due to disturbance of the gastro-intestinal tract and other direct irritative symptoms have more or less subsided. A number of cases have been described, however, in which transitory palsy appeared within a few hours or a very few days, and in rare instances even severe paralysis has begun to develop within three or four days after the acute poisoning. On the other hand, the paralysis may be delayed several weeks, and the patient may show no symptoms in the interval following the acute symptoms. Paralysis has even been delayed for a year (Perkins), the interval in this instance having been filled with distressing pains. In chronic poisoning the time of appearance of paralysis depends, of course, upon the dose, and upon individual susceptibility. It has developed after three or four weeks' use of arsenic, but, naturally, it often appears much later.

Paralysis is usually preceded by disturbances of sensation. Contrary to the conditions in lead palsy, paræsthesias and particularly pain are very common. Pain is strikingly frequent and extremely distressing, both before the paralysis appears and for some time after it has developed; its frequency and severity constitute, indeed, important indications of arsenic poisoning. The nerve trunks, also, are frequently sensitive to pressure, and the skin may be extremely hyperalgesic upon touch or pressure. With the progress of the palsy, all qualities of skin sensation become reduced or lost, the legs and feet usually showing the most marked changes. Curious anomalies of sensation—polyæsthesia, allochiria, etc.,—have been seen.

Motor palsy usually develops subacutely in cases which follow acute poisoning; in rare instances it appears very suddenly. It may, however, develop slowly even when due to acute poisoning, and in chronic poisoning this is generally the case. Like the anæsthesia, it is most marked and most common in the legs. Writers who have collected large series of cases agree in the statement that the legs are almost always affected, that they are often paralyzed when the arms are not, and that they frequently suffer alone. The paralysis has, however, a marked tendency to involve

all extremities. The motor and the sensory palsy alike affect the distal portions of the extremities, and very rarely extend above the knees and elbows; while the upper arms, the thighs, the trunk muscles, and the sphincters, escape. Both the extensors and flexors are involved and there is no tendency to spare certain muscles as in lead palsy, all muscles of the areas affected suffering. The extensors are, however, usually more severely diseased than the flexors. It is very unusual for the arms to be affected without the legs, and paralysis localized to one extremity is rare, though it has occurred.

The knee-jerks are almost always lost when palsy is at all marked. Degeneration reactions are present, and the response to faradism is reduced or lost. Atrophy develops within a few weeks and often becomes extremely marked. Contractures of much severity are frequent when well-developed poisoning has been present for some time.

Cases of rapidly fatal progress are almost unknown, but the disability that develops may be extreme and death may occur with the appearances of general cachexia. Unless, however, the paralysis is very severe or has been long neglected, improvement usually begins after a few months at most, and it progresses in most cases to complete or almost complete recovery, though occasionally marked disability remains permanently.

In very rare instances, single cranial nerves have been diseased alone; aphonia from laryngeal paralysis has, for example, been reported by Morell Mackenzie and Brouardel; ptosis has occurred and other external eye muscles have been paralyzed. Lagophthalmus has been described. Amblyopia and amaurosis occasionally appear. Cloudiness of the lens has been reported after acute poisoning, and is said to occur as a result of chronic poisoning.

There is an interesting and important group of cases to which attention was directed by Dana,¹ in which ataxia, particularly of the legs, is so conspicuous a feature that it may readily lead to a diagnosis of tabes dorsalis, unless the mode of onset, the presence of neuritis, and the absence of involvement of the sphincters, are carefully noted. Psychic symptoms sometimes occur, more especially in severe and prolonged cases. They are chiefly loss of memory and general weakness of intellect that may progress to pronounced dementia. Sometimes hallucinations are conspicuous.

Diagnosis.—If a source of poisoning is recognized and the nature of the case thereby suggested, there is, as a rule, little difficulty in diagnosis. With skin lesions particularly, and more especially with keratosis or pigmentation, arsenic should be considered and a source sought for. If suggestive symptoms develop in a patient who has been under treatment for chronic skin disease, malaria, anæmia, glandular enlargement, chorea, or other disorders in which arsenic is frequently used freely, the possibility of poisoning should always be suspected. This will, of course, occur to the attendant if he is himself giving arsenic. The pains, since they may occur without any paralysis, or may long precede paralysis, are likely to be mistaken for neuralgia dependent upon other causes, or be put under the crude class of "rheumatic pains." These mistakes are avoidable only by a proper investigation of the nature of any persistent pains.

¹ *Brain.*, vol. ix, 1886–87.

The paralysis may have to be distinguished from lead palsy, alcoholic neuritis, and neuritis due to various infections and other causes. Lead palsy is usually readily excluded by the severe pains and other sensory disturbance, the more marked involvement of the legs than the arms, the distal localization, and the paralysis of muscles that escape in lead poisoning. The other conditions will be excluded, as a rule, only by finding a source of arsenic, or by searching for arsenic in the urine. If a person who has no history of alcoholic or infectious cause for a neuritis, develops peripheral palsy, particularly associated with severe pains and the other characteristics of arsenical paralysis, a source of arsenic should be carefully searched for, and the urine should be examined for it. A negative result of the latter examination is not distinctive, for arsenic is not constantly present in the urine even when it is in the system, and it is usually entirely excreted within about two weeks of the time that ingestion ceases; for the latter reason, it may have permanently disappeared from the urine, even though severe symptoms are still present. A distinctly positive result by Reinsch's test is of much importance; this test may be carried out by any one who has a little skill in laboratory technique; 500 to 1,000 c.c. of urine should be evaporated at a low temperature to about one-fourth the original bulk; one-fifth part of hydrochloric acid, free from arsenic, and a piece of copper foil, are added and the fluid boiled for fifteen minutes. If arsenic is present the surface of the copper becomes grayish, or, if there is a large quantity, it turns a deep blackish-gray. The fact that arsenic is present may then be definitely determined by the sublimation test, which gives a crystalline mirror of arsenious acid. If this test gives a doubtful result, a trained chemist must be called in to decide the question.

Cases due to arsenical wall paper, carpets, dress goods, etc., are now very rare; the diagnosis will depend solely upon chemical investigation of suspicious objects and of the urine. In this class the symptoms have often been obscure, and if so, whatever the source of the arsenic, the diagnosis is likely to be suspected only in case there is a careful consideration and search for all possible causes of the disorder.

Prognosis.—The main points concerning the course of the poisoning have already been discussed. General symptoms, unless very severe and protracted, usually disappear gradually if properly treated; and, if the poisoning ceases, the skin disorders are usually recovered from, though often slowly. Keratosis or ulcers occasionally become epitheliomatous or run a very long course in spite of exclusion of the cause. Pigmentation, as a rule, greatly improves or disappears, though at times disfigurement remains permanently. The nervous symptoms are, in general, of good prognosis; like all toxic paralyses, however, those due to arsenic are occasionally permanent, or show little improvement if they have reached a severe grade, and especially if treatment is long delayed. Marked psychic symptoms are unusual; since they are commonly due to advanced or protracted poisoning, they are of very doubtful prognosis but severe stages may be recovered from.

Prophylaxis and Treatment.—The prophylaxis of industrial poisoning should follow the principles discussed under lead poisoning. When these are properly used they prevent a very large proportion of the evil results. Intoxication from therapeutic use of arsenic can usually be avoided by

care in administration; even in diseases such as pernicious anæmia, in which large doses are often necessary for a long time, severe symptoms can be prevented by watching for gastro-intestinal disturbance, signs of renal irritation and, particularly, by observing slight pigmentation and other mild chronic toxic effects.

The treatment must be regulated according to the conditions to be cared for. Potassium iodide in moderate doses, 5 grains (0.3 gm.) after meals, is generally considered a useful eliminant, but there is no specific treatment. Skin lesions should be managed in accordance with the individual case, and paralysis should be treated as multiple neuritis is treated. In the earlier stages of the latter, pain will frequently be a troublesome feature, and will require symptomatic treatment, the extremities being protected from pressure of bedclothes, etc., the pains controlled by warm applications, hot baths, or if necessary, coal tar preparations or opiates. Rest is essential until all irritative symptoms are past. Carefully graduated massage, electricity, and passive movements, with slowly increased active exercise, must be used persistently. Avoidance of alcohol and careful regulation of the hygiene of life are to be insisted upon.

CHAPTER VII.

OTHER METALLIC POISONS, MERCURY, PHOSPHORUS, ETC.

By DAVID L. EDSALL, M.D.

CHRONIC MERCURY POISONING.

UNDER this heading will not be considered the acute and subacute symptoms included under the term ptyalism, but only those disorders that are of more direct interest to the medical clinician.

The fact that mercury, besides causing ptyalism, may produce chronic poisoning has certainly been known since the early part of the Christian era and it has been recognized in medical writings for at least twelve centuries. Maréchal, in reviewing the history of chronic mercurialism, refers to distinct medical evidence that it was known as far back as 850 A. D.; and according to Dieterich, Rhazes recognized clearly that it may produce nervous symptoms. Lively interest in the subject was not awakened, however, until the controversy between the mercurialists and the antimercurialists, in the sixteenth century, showed its importance; and the first distinct description of tremor, disturbance of speech, and other nervous disorders, as direct effects of mercury, is said by Maréchal to have been written in 1519, by a layman, the chevalier Ulrich von Hutten, who observed them in his own person as a result of treatment for syphilis. In such cases even to the present time, there is doubt whether the symptoms were due to the mercury or to the syphilis; but Fernel, in 1557, described a case in which chronic poisoning occurred in a man who was not syphilitic and who had not taken mercury medicinally, but who had worked with the metal. Occupational poisoning, with nervous symptoms, was recognized by Ramazzani. Jussieu, in 1719, described the conditions in the mines at Almaden; Astruc, in 1738, contributed an elaborate and valuable description; and in the century that has just passed, there were numerous observations and studies, among which that of Kussmaul is classical.

Etiology.—The importance of chronic mercurial poisoning has largely decreased in recent years, partly because much greater care is now exercised in using mercury medicinally, but much more because in a number of industries in which mercury poisoning was once common, this metal is not now used, or the industries themselves have given way to others that accomplish the same purpose. In mirror making, for example, mercury has been replaced by silver; and fire gilding and silver plating with the aid of mercury have almost or quite disappeared, electroplating and roll

plating having taken their place. Besides the occupations mentioned, the preparation of mercurial pigments, their use in paints, in the making of artificial flowers, dyes, etc.; the use of amalgams in making gold and silver jewelry; the exhausting of incandescent light bulbs with mercury pumps; the preparation of fulminate; the manufacture of fireworks; the production of some aniline colors; and the preparation of the skins of animals and birds, has produced chronic poisoning. Mercury has been used in all these processes, and in some parts of the world is still used in many of them. Most of these occupations, however, are at present of very little consequence in this regard.

The chief industries in which this poisoning is now seen are mercury mining and smelting, the manufacture of thermometers, barometers, and other physical apparatus of which mercury is an essential part, and the manufacture of felt hats, the acid nitrate of mercury being used in the latter in treating the felt.

Mercury mines have long been recognized as a fruitful source of salivation and chronic poisoning: the mines at Almaden and Idria have furnished the basis of a goodly part of the literature on this subject, and there have always been many cases among those working in mercury mines. It is even stated that those living near the mines, but not working in them, sometimes show chronic poisoning, and it is said that through a fire in the Idria mines in 1803, the atmosphere in the surrounding regions became so laden with the vapor of mercury that nine hundred or more persons exhibited mercurial tremor. Since mercury volatilizes at ordinary temperatures, this danger could be controlled only by ventilation that is constant and thorough, an exceedingly difficult problem in mercury mines. Dr. Jamison, of New Almaden, California, states that poisoning is still very common among the workmen in the great mines there, but is less so than it was, partly because the ore is less rich. Among special sources of salivation, which may also be sources of chronic poisoning, he mentions drinking water about the mines, which is usually charged with the metal, entering a drift too soon after a blast, when the air is filled with fine particles of mercury, and standing over the furnaces to free them of wet ore that has become clogged. Because of the comparatively small number of men employed in mercury mining, this source of poisoning is of limited clinical importance, and the restriction of this industry to a few places also serves to make it of relatively little importance to the profession at large.

In this country there are but a few persons who are exposed. However, these occupations are of much interest to the medical clinician when he comes in contact with them, because a considerable proportion of those exposed develop more or less severe chronic poisoning, and also because proper hygienic arrangements will prevent a very large percentage of these cases.

Hat making, because of the comparatively large number of persons employed at it and because of the fact that it is a widely distributed industry, is of more direct interest to the profession in general. It has been impossible to obtain any satisfactory figures as to the number of persons in this industry who are exposed to mercury poisoning; it is generally known, however, that many cases of poisoning occur. A few years ago at the Episcopal Hospital, Philadelphia, employees from one factory fre-

quently appeared in the out-patient department or in the wards; they are now cared for by special provision of the proprietors of this factory. The danger occurs in handling the felt after the solution of acid nitrate of mercury, with which it has been treated, has dried; and poisoning occurs chiefly through the dissemination of small particles of dust in the course of cutting and fitting the felt, etc., possibly also through some volatilization and through the skin in handling the felt. Chronic mercurialism also occurs among men engaged in the production of various salts of mercury in chemical plants, though to what extent is difficult to determine. Salivation is not uncommon among them and chronic poisoning must occur occasionally, but it is probably quite rare.

Poisoning from the medicinal use of mercury occurred not infrequently until the danger became thoroughly and generally recognized. At present, chronic mercurial poisoning of this source is extremely rare. It is almost always preceded by more or less pyalism, and this is of course sufficient to lead almost certainly to the withdrawal of the drug before chronic mercurialism appears.

Accidental intoxication very rarely occurs now, but it has developed in most curious and interesting ways. One of the most striking of these is the story of the ship "*Triumph*," that in 1810 sailed with a cargo including much mercury that was held in containers; some of the latter burst, and in three weeks, it is said, many of the persons on board had some of the phenomena of chronic mercury poisoning. There are also on record instances of persons having been poisoned by living in buildings where mercury was used for industrial purposes, even when their living-rooms were separated by several stories from the workrooms; and there is an instance in which persons who lived in a tenement developed mercurial poisoning, which investigation showed to be due to the fact that the rooms had previously been used as a mirror factory. In the last mentioned series, the mercury had dropped through cracks in the floor and its continual volatilization produced the poisoning; much mercury was discovered when the floor was torn up. The previously mentioned widespread poisoning from the fire in the Idria mine is another striking instance of accidental poisoning.

Pathology.—So little work has been done on the pathology that it cannot be satisfactorily discussed. Wising has described degeneration and atrophy of the myelin in the lateral columns of the cord and reduction in the number of fibers, and Brauer has noted, experimentally, degenerative changes in the cells of the anterior horns, using the Nissl stain. Letulle and Heller describe experimental neuritis after sublimate injections, but Brauer considers this to have been due to the local effects of the injections, not to the general action; and it is probable that chronic mercury poisoning rarely or never produces neuritis. Prolonged medicinal use, and sometimes occupational poisoning, may cause anæmia and marked emaciation, with more or less severe fatty degeneration in various organs, and chronic gastro-enteritis is quite a common result. The occasional anæmia and cachexia, the profound changes sometimes seen after severe acute poisoning, especially in the kidneys and bowel, and the remarkable influence of mercury on syphilitic tissues show that it may exert an extremely important effect upon nutritive processes. C. W. Miller and the writer recently studied the influence upon autolysis and have contrib-

uted evidence that mercury increases autolysis. Probably this is one way at least in which the metal acts upon nutrition.

Mode of Entrance.—There is overwhelming evidence that mercury may enter the system through inhalation as vapor, and it is probably the chief way in which occupational poisoning occurs, though absorption through the skin seems to play a role of considerable importance; and in the manufacture of hats, the preparation of skins, and similar processes in which much dust is created, inhalation of actual particles occurs. There are always ready opportunities for inhalation poisoning when mercury itself is used, since it volatilizes at ordinary temperatures, and furthermore the heating processes necessary in most of these industries largely increase the volatilization. Frequent ingestion of small particles is probably a factor of much importance, even in occupational poisoning. Workers in mercury, like others exposed to similar dangers, grow surprisingly careless, and one may see them eating food or fruit, or smoking cigars or pipes, on which there are visible globules of mercury; the superintendent of a large thermometer factory directed the attention of the writer to the fact that those whose work-tables were kept neat and who were careful as to cleanliness of the person escaped poisoning in a large proportion of cases, even though engaged in especially dangerous parts of the work.

Symptoms.—It is a striking and generally recognized fact that salivation and stomatitis are very often absent in the chronic cases. In examining the mouths of a series of cases in which there were marked nervous symptoms, the writer found in almost every instance that the gums and teeth were in fairly good condition for persons of their social class except that, as is often the case in mercury workers, the teeth showed blackish discoloration. Sometimes, however, persistent pytalism does develop, generally before the nervous symptoms. In the early stages of poisoning and when the condition is more pronounced, the patients often complain of headache, restless sleep and marked depression and weakness, particularly in the morning; the latter sensation may pass off later in the day so that they often feel quite well toward evening. Several subjects of mild poisoning stated that they had a most abnormal dread of the exertion of going to work in the morning; later on, this passed off and the remainder of the day they felt entirely cheerful. Sometimes anæmia develops and, in severe cases, a condition of general cachexia occasionally appears. Gastro-intestinal disturbance, particularly of the stomach, is also not uncommon, though less frequent than one would expect. Neuralgic pains, especially in the territory of the trigeminus, are quite common in both early and advanced stages and joint pains also occur. Dr. Jamison has frequently seen loss of sexual power, which usually improves upon treatment.

But the most striking and common features of chronic mercurial poisoning are the tremor and the emotional disturbance or erythism. These are usually associated with each other in greater or less degree from the beginning. The tremor in early stages is absent when the subject is quiet but appears upon voluntary effort, especially upon finely coördinated movement; and emotional influences usually have an intense effect in increasing the tremor, bringing it out when not otherwise present. For example, upon attempting to write his name, particularly in the presence of witnesses, a

man who is ordinarily free from tremor but who is in the early stages of poisoning may develop tremor at once. This may be slight and of small amplitude, but is more likely to be rapid, gross movement, and is frequently so severe that it at once becomes wholly impossible for the man to write legibly. After a few moments the tremor and excitement decrease and within a short time they have nearly or quite vanished. The hands and lips are chiefly affected at this stage and usually more severely than other parts at all stages; if the condition is marked, however, most of the facial muscles are involved and all the extremities frequently show tremor. All grades of severity may be seen, and the phenomenon in bad cases is most remarkable. When the tremor has grown actually troublesome it is ordinarily present in some degree even when the patient is at rest; it may be constantly very marked and in extreme cases may interfere with almost all coördinate muscular action; the patient may become unable to feed himself or to stand, and cases have been described that were of such severity that the patient had even to be strapped in bed to avoid injury from the violent and general movements. Frequently, however, the tremor is comparatively slight at most times, even though the response to muscular action or emotional excitement is very severe. For instance, without his knowing, the writer watched a man blow spherical thermometer bulbs of various sizes that were necessarily very accurately graduated. He had slight tremor but it did not interfere with this fine work, but when spoken to, he instantly went into general tremor; he could then scarcely hold the tubing in his hands, the lips, facial muscles, and orbicular muscles showed violent twitchings and contortions, and there was general severe tremor of the body and legs which were so marked that had he not been sitting he would have dropped to the floor. A few minutes later he was calmly at work again. The tremor in bad cases may persist during sleep but often does not.

Physical examination, even in severe cases, usually shows nothing beyond the tremor except, perhaps, slight or moderate muscular weakness. Occasionally weakness is very marked even when other symptoms are absent. Nystagmus has been described but is very rare. A point of importance and one that has sometimes caused confusion with multiple sclerosis is that owing to the involvement of the muscles of articulation the speech is frequently much disturbed. It may be of somewhat the same irregularly staccato type seen in multiple sclerosis; but it is usually evident that the disturbance of speech is due merely to the severe tremor of the lips and facial muscles. Another point that sometimes lends resemblance to multiple sclerosis is the fact that vertigo is a frequent complaint and at times is so severe as to cause the patient to fall.

Sometimes there are choreiform movements, chiefly in severe and advanced cases, and in the same type, disturbances of sensation—usually anæsthesia—may sometimes be seen. Paralysis also occasionally occurs in bad cases; it is likely to be localized and incomplete and is often not permanent. Choreiform movements, anæsthesia, and paralysis are likely to be irregularly distributed and limited to one extremity or to one side.

Convulsive attacks are described and may be of true epileptic type, though it is not certain that epilepsy is ever due to mercury. Two other forms of convulsions have been attributed directly to mercury. One of them is tonic and follows violent movements or hard work and affects

chiefly the flexors of the forearm. This tonic spasm comes on chiefly in painful paroxysms but may persist to some extent in the interval. During the attack the patient grasps anything at hand with all his might, and at the end of the spasm he is often for some time unable to let go. In the other type the convulsions are clonic and of the form described by Rous-sel as occurring somewhat frequently at Almaden and called there *calambres*. These occur in paroxysms that are said to have some likeness to malarial chills. There is marked oscillation of the head with movements of the eyelids and eyeballs, the facial muscles, and the arms and legs. The violence of the attacks at times makes it necessary for several persons to hold the patient. The attacks are often painful but there is no loss of consciousness. A large proportion of the subjects of these are said to die within a year after the attacks appear.

In addition to the disorders mentioned, neuritis has been described. Leyden discussed it in 1893; Remak narrows down Leyden's cases to at most three that are reliable and even these seem to me somewhat doubtful as direct results of mercury because of their association with violent dysentery in two and with gastro-enteritis and gonorrhœa in the other instance. A few cases have been described in which there was severe ataxia. Kussmaul has described aphonia from laryngeal paralysis but this is extremely rare. There may be exaggeration of the special senses; the least noise, for example, may be intensely disagreeable. Shivering feelings and sensations of cold are common.

The chief other disturbance is of the emotional nature. This is closely associated as a rule with the tremor. Sometimes, however, it is very marked when there is little or no tremor, or it may be very inconspicuous as compared with the tremor. Most of the patients notice this emotional disturbance before anything else; many of them describe it by saying they first notice that they have "lost their nerve." Any sudden occurrence, even of the most trivial nature, throws them into tremor, usually accompanied by a sudden sense of powerlessness, or of fright. In bad cases the feeling of weakness causes the patient to drop into the nearest seat or grasp the nearest support, lest he should fall. These persons come to dread the least disturbance and they often avoid company because little conventionalities bring on this embarrassing excitement; several men have stated to the author that they would walk around a block if they saw a friend on the street because they dreaded the mere sign of recognition in passing. At first their attitude toward this disturbance is merely one of perfectly natural annoyance with themselves because of what they term their own silliness; later they may become morbid, and in severe and advanced cases may develop a distinct psychosis, which varies in nature but seems usually to be dementia. Actual psychosis seems, however, to be rare now; its frequency has probably decreased since Kussmaul made his classical study, improved hygiene being chiefly responsible for this.

The relation of this emotional disturbance to hysteria is interesting, particularly in regard to the question whether hysterical symptoms are directly due to a toxic agent, or are dependent upon a psychic anomaly in the individual and are merely brought out by some toxic agent. Certainly if these symptoms in mercurial poisoning are due to an essential anomaly in the individual, this anomaly must be pretty widely distributed; it looks rather in this instance as if the poisoning produced the symptoms

directly, for they occur in an extremely large proportion of cases. In examining and questioning a series of patients who showed various degrees of chronic poisoning, the same emotional condition was usually found, and yet nearly all were well-built, healthy-looking men, who in other respects showed not a shade of the appearance of hysteria.

Diagnosis.—The chief conditions that are likely to cause confusion are disseminated sclerosis, paralysis agitans, general paresis, alcoholism and lead poisoning.

The nature of the occupation and the knowledge and determination of the fact that mercury is used, if necessary the demonstration that mercury is present in the urine, are the most important points, and as a rule, settle the diagnosis pretty thoroughly. The wide amplitude and irregularity of the movements, the remarkable effect of emotional influences, the absence of nystagmus and of any evidence of focal cerebrospinal lesions, and the strikingly tremulous and emotional character of the stammering, distinguish the condition from multiple sclerosis. The rapid appearance or marked increase of the tremor upon movement or emotional stimulus, the lack of persistent rigidity and of the peculiar expressionless appearance of the features separate it from Parkinson's disease. General paresis is excluded by the absence of focal signs of cerebrospinal changes, and by the lack of delusions of grandeur and changes of the moral sense; also by the fact that tremor is usually by all means the most pronounced feature. Frequently alcoholism is actually associated with mercurial poisoning; in such cases the very severe tremor, the peculiar erythsm, and the extremely marked influence of the latter upon the tremor indicate the double poisoning. When alcoholism is not present it may be excluded by the history and by the absence of all signs of it except tremor and excitability, and the last mentioned features differ in the two conditions. Lead poisoning will almost always be indicated by the occupation, by attacks of colic and by the blue line, even if evidences of characteristic lead neuritis are absent. Basic degeneration is also probably an important distinction, but this has not been definitely determined in relation to chronic mercurial poisoning. Lead poisoning and mercurial poisoning may be combined, but this is unusual; in such cases it is necessary to determine that mercury is used in the work or is present in the urine.

Prognosis.—If the tremor has not become constant and there is no marked cachexia, recovery practically always occurs under proper surroundings. Even severe and persistent tremor usually disappears ultimately, as does the emotional disturbance. If there is paralysis, mental disturbance, or severe cachexia, the outcome is doubtful. Sometimes even moderate tremor never wholly disappears, and in any instance recovery is likely to be very slow. Prognosis depends largely upon freedom from further exposure and upon abstinence from alcohol and excesses of all kinds. Some persons have recovered from very marked symptoms while continuing at the same work, but this was only when unusual care was exercised, and as a rule is not possible.

Prophylaxis and Treatment.—As in almost all similar conditions, the majority of cases of poisoning can be prevented if employers properly protect their workmen. The results of the energetic and successful efforts of Wollner in enforcing proper hygiene in the mirror factories at Fürth

are profoundly impressive in this regard. Thorough ventilation is the most essential point, as is shown by Wollner's experience. A large manufacturer who is interested in two factories, one old and with poor hygienic arrangements, the other new and well-ventilated, states that men have acquired severe chronic poisoning in the old factory and have recovered in the new while doing the same work. Cement floors and other forms of construction that permit of thorough cleanliness and prevent the accumulation of particles of mercury, the use of hoods whenever possible and of well-covered containers for the mercury, with the requirement that the employees shall be extremely careful to cleanse themselves before eating, to cleanse their persons thoroughly, and to protect their hands with rubber gloves while at dangerous work, are also of the greatest importance. Free and nutritious diet, abstinence from alcohol and from sexual and other excesses, with a generous amount of exercise, in the open air, if possible, are of the utmost value in prophylaxis and treatment. Many workmen take small doses of potassium iodide at frequent intervals as a prophylactic, particularly if they have already had slight symptoms, and a number have recovered from marked poisoning without cessation of work by treating themselves in the manner indicated. Turkish baths and frequent hot baths are also useful.

The measures mentioned are the most important in any stage of poisoning, as well as in prophylaxis. Sometimes the severity of special symptoms particularly the tremor, may demand medicinal treatment. Sedatives such as derivatives of opium, chloral, bromides, and also belladonna and pilocarpine have been found useful. Musk has been very highly praised by some authors of experience.

PHOSPHORUS POISONING.

The history of phosphorus poisoning practically begins with the invention of phosphorus matches in 1833. A little more than a decade later the descriptions of Lorinser, Heyfelder, Strohl, and particularly of v. Bibra and Geist, of the distressing effects of phosphorus upon workers in match factories, aroused most intense interest, and their studies, together with others that followed, have resulted in some of the most remarkable advances in the history of humanitarian industrial reforms. A number of European countries have forbidden the use of poisonous white or yellow phosphorus in making matches, and, as a consequence, non-poisonous matches are now made in enormous and increasing numbers in these and other countries. Business sagacity and philanthropy have led in this country as well as in Europe to marked improvements in the hygiene of match factories and the care of the health of the workmen; in Europe legal enactments have, to some extent, enforced such measures; the result is that the danger in many plants that still use white phosphorus has been greatly reduced and in some it has almost disappeared. Clinical interest in chronic poisoning has, therefore, become greatly lessened.

Acute phosphorus poisoning has likewise come to be largely past history as a matter of clinical importance in most parts of the world, and it never was of much consequence in this country. Hence phosphorus poisoning demands but brief discussion. Acute poisoning is still common

in a few countries, such as Sweden, and among cities Prague has a most unfortunately large recent record of deaths from this cause. Phosphorus necrosis also still occurs with some frequency in a small number of European countries in which workmen have little or no legal protection and the hygienic conditions are poor. It is not improbable that cases occur in Japan, where matches are manufactured in large quantities. In general, however, both acute and chronic cases are now few, and the industrial cases are chiefly cared for by specially trained medical employees of corporations, so that the subject is of little interest to the general profession.

Etiology.—Industrial (chronic) poisoning has occasionally occurred in the manufacture of phosphorus itself, but is almost always due to the much more dangerous exposure that occurs in the use of the crystalline white or yellow phosphorus in making matches. Phosphorus, of course, volatilizes at room-temperature, and in dipping and packing the matches, exposure to the vapor inevitably occurs unless the workrooms are large, extremely well-ventilated, and kept scrupulously clean. The most serious results have occurred in the small and wretchedly-equipped house industries of European countries, which are now fast disappearing, but larger factories with poor equipment have naturally furnished many cases. The degree to which the danger may be overcome is shown by the experience of Dr. Knowlton of Akron, Ohio, who has charge of over two thousand employees of one company. This company now provides commodious workrooms that have excellent ventilation and are kept thoroughly clean; separate eating rooms are also furnished, the employees are given facilities for personal cleanliness, and much of the work previously carried out by hand, is now done by machinery. The condition of the mouth and teeth of the workmen is rigidly inspected and local disease is at once treated and the subject removed from further danger. Dr. Knowlton writes that he has at present in this large number of employees only two cases of necrosis and these are mild. A general idea of the earlier as well as the present conditions in other countries may be obtained from *Dangerous Trades*, the publications of the British Home Office, and the articles of Bauer, Hölzer, Kaup, G. H. Wood and others in *Gesundheitsgefährliche Industrien*.

"White" phosphorus, which becomes "yellow" phosphorus on exposure to light, forms amorphous "red" phosphorus if subjected to a high temperature in an atmosphere free of oxygen. This red phosphorus, which is used in making most safety matches, is almost harmless to those working with it, even if swallowed, apparently because of its slight volatility and solubility.

Accidental chronic poisoning has been reported in rare instances, for example, as a result of the phosphorus vapor produced by storing a large number of matches near a stove. Purely accidental acute poisoning has occurred in a few cases, but as a rule is due to attempts at suicide, generally by swallowing match heads. Children have also unknowingly poisoned themselves with matches; twenty-five match heads usually contain enough phosphorus to cause grave or even fatal poisoning of an adult. The very large doses of phosphorus that were once recommended for therapeutic purposes, especially in treating rickets, caused fatal poisoning in a number of instances. Finally, Kobert has suggested that some cases

of icterus gravis, or acute yellow atrophy, may be actual instances of phosphorus poisoning resulting from reduction, chiefly in the intestinal tract, of the phosphorus compounds contained in such substances as lecithin and nucleins. He and others have conducted interesting experiments concerning this point, but have not as yet demonstrated its truth.

Pathology.—Experimental chronic poisoning has produced hepatic cirrhosis and chronic interstitial nephritis. The result of chronic poisoning in human subjects is almost always necrosis of the jaw with subsequent sequestrum formation and suppuration of the bone and the nearby tissues, the lesions being very extensive in cases not treated early. General fragility of the bones has been described.

The changes in acute poisoning have led to some of the most important observations and experiments in the history of pathology. In brief, they are reduction or loss of coagulability of the blood, diffusely scattered small or larger hemorrhages, icterus, loss of elasticity of the vessels, fatty changes in the muscles, heart, kidneys, stomach, and duodenum, enlargement of the spleen, and very extensive changes in the liver; the latter organ is enlarged, of saffron color, a typical fatty icteric liver, the acini, large and easily seen, and microscopically there is an extensive deposit of fat, while some of the liver cells are merely filled with fat, others are undergoing destruction or have been entirely destroyed. Much work has been done on the question of the source of the fat by Lebedeff, Pflüger, Athanasiu, A. E. Taylor, Kraus, Sommer, and others, and it is now fairly clear that it does not come from transformation of protein into fat, but from deposit of fat that is transferred from depots elsewhere. If, as has often been the case, the phosphorus is taken for the purpose of producing abortion, there are usually hemorrhages into the cavity of the uterus, there is frequently abortion, and the organs of the foetus may show the same changes as those of the mother.

The alterations in the chemistry of the organism are very striking and their study has led up to a considerable part of a body of knowledge that has caused profound changes in the teaching concerning many normal and pathological processes. Oxidative processes are reduced, as are synthetic processes, such as glycogen production in the liver and muscles, and the supposed synthesis of hippuric acid by the kidneys, while the work of Jacoby has shown a marked increase of autolytic processes. Intermediate products of metabolism in abnormal amounts or substances that are entirely abnormal—leucin, tyrosin, cystin, sarcolactic acid and peptone-like or ptomaine-like substances—are found in the blood and urine; glycosuria often occurs; there is very excessive acid production and the power of oxidizing acids is reduced. As a consequence, the ammonia of the urine is greatly increased while the urea is diminished. The last-mentioned conditions are due chiefly to the acid intoxication, not to the loss of the liver's function of producing urea.

The action of phosphorus seems, as was stated in 1869 by Schultzen and Riess, to be like that of a ferment: in what manner its results are produced, whether through furtherance of the effects of bacteria or of their growth, or through exciting processes that are normally resident in the cells, is not wholly certain, but recent knowledge makes it much more probable that its chief action is to accelerate certain ferment processes.

Symptoms.—Acute poisoning bears a very close resemblance to “idopathic” icterus gravis and acute yellow atrophy; it is therefore of much interest to the medical clinician in the few regions where it occurs frequently. Some hours after taking phosphorus, vomiting and often diarrhœa appear; and the vomitus may be phosphorescent. The symptoms remit after the digestive tract is emptied, and for two or three days the patient seems almost or quite well. After this, vomiting returns and icterus develops, as do epigastric pains, tenderness of the whole trunk, and distressing pains in the muscles, which are probably in large part the result of hemorrhage into the tissues. Blood is often present in the vomit and stools, and petechiæ occur in the skin and mucous membranes. The liver enlarges a day or two after the return of the symptoms and grows tender; later it may decrease in size, but usually it does not unless recovery occurs. The patient becomes apprehensive, sleepless and prostrated. There is much less tendency to severe cerebral disturbance than in acute yellow atrophy or icterus gravis, but, in some instances, marked somnolence, coma, or maniacal excitement appears a day or two before death.

Phosphorescence of the breath and urine has been described, apparently with somewhat doubtful accuracy. The urine, when poisoning is well developed, contains much sarcosine, at times leucin, cystin, occasionally tyrosin. The ammonia of the urine is greatly increased, the urea is usually diminished; the total nitrogen excretion is ordinarily increased beyond the intake.

In fatal cases, the end generally occurs after about a week, sometimes earlier. Fully half the cases die. If recovery takes place the symptoms gradually subside, the liver decreases in size, and it may ultimately shrink to less than its normal dimensions. There may be sequelæ such as neuritis and paralysis from cerebral hemorrhage.

Chronic poisoning consists almost entirely of necrosis of the jaw and neighboring tissues, and the consequences of this local disease. General disturbance of health without necrosis is described by some observers, but is not conspicuous at best. Necrosis occurs particularly in those whose mouths and teeth are in bad condition; it is not the effect of phosphorus alone, but of bacterial action also, and hence conditions that favor bacterial growth favor necrosis. It begins usually about a single tooth, most commonly in the lower jaw, with local decay and abscess formation. If not treated quickly, the disease spreads and the gums become loosened. If the tooth is removed, exceedingly foul pus is discharged from the alveolus, the necrosis advances to neighboring teeth and to further portions of the jaw-bone, sequestra form, the suppuration extends to neighboring tissues, sometimes burrowing deeply into the neck, frequently breaking through the skin; the patient becomes weak and anæmic and is likely to develop amyloid disease, phthisis, basal meningitis, or general septicæmia. Frightful disfigurement has been produced in some cases, and, with the dreadful odor, has made the subjects almost outcasts. Occasionally other bones besides those of the jaw become necrotic, and instances have been reported in which ten or more of the cranial bones were involved. A series of cases is on record in which there was general fragility of the bones, and this was believed to be due to phosphorus; in some cases, also, wounds involving bones of the limbs

have been followed by necrosis of these bones. It has been repeatedly observed that necrosis may make its first appearance even years after the subject has ceased working in phosphorus. If local treatment is instituted very early the necrosis is sometimes controlled without serious surgical measures; and if the disease is distinctly developed but not advanced, resection of the bone usually checks it. In severe cases even extensive surgical measures may not stay its progress.

Diagnosis.—Acute poisoning is distinguished from acute yellow atrophy chiefly by the history of poisoning; by the appearance of jaundice, and of other severe symptoms two or three days after temporary gastric symptoms, while in acute yellow atrophy, the grave symptoms are usually preceded for some time by signs of catarrhal or obstructive jaundice; by the enlargement of the liver; by the fact that leucin, and more particularly tyrosin, are less common and less abundant than in acute yellow atrophy. Cerebral symptoms are also much less frequent. None of these distinctions is absolute or constant. Phosphorus necrosis is diagnosed chiefly by means of the occupational history, with persistent and advancing necrosis of the jaw.

Prognosis.—Acute poisoning is always very grave, one-half or more of the cases ending in death. The prognosis depends largely upon the promptness with which the stomach is emptied and further treatment instituted. If severe symptoms develop, it depends upon their duration; with each day beyond three or four that such symptoms continue, the outlook grows much more grave. The course of necrosis depends upon the rapidity and thoroughness of treatment. Early resection is usually successful. Advanced disease and long-postponed treatment renders the prospects doubtful as to recovery, and, at best, the disfigurement is likely to be severe.

Prophylaxis and Treatment.—Phosphorus necrosis would practically disappear were the use of white phosphorus in making matches everywhere forbidden. While this has been done in several countries, it is doubtful whether it can ever be generally carried out with success, and at present it certainly cannot. Constant and thorough care of employees' mouths and teeth and of the hygienic conditions in the workrooms, with the use, whenever possible, of machinery in place of handwork, will, as shown by recent records here and in England, almost entirely prevent serious results.

The treatment of the necrosis consists in removing the subject from danger upon the development of the slightest signs of necrosis, immediate dental treatment of the local disease, and, if it does not yield, or advances in spite of this, early resection of the jaw. Acute poisoning should be treated by the immediate administration of copper sulphate, both for its emetic effect and because it forms a coating over the phosphorus match heads and prevents much of the absorption. The stomach should be washed out, using potassium permanganate solution (2 per cent. to 3 per cent.) or hydrogen peroxide (1 per cent. to 3 per cent.) for their oxidative action, since the oxides of phosphorus are little, if at all, poisonous. If diarrhoea is not present a purge should be given, avoiding castor oil since oils increase the solution of phosphorus. Old, ozonized turpentine should be given in doses of 0.5 c.c. ($7\frac{1}{2}$ m.) three or four times daily for a week or more, as it is supposed to favor oxidation of

the phosphorus. Alkalies should be administered. If there are severe symptoms, the dose of alkali should be very large in order to combat the acid intoxication, and intravenous administration of alkalies may be used as in diabetic coma.

CHRONIC SILVER POISONING OR ARGYRIA.

Argyria is of two forms, local and general. The former occurs in those who handle silver in their occupations, when it is seen chiefly in the skin of the hands, a condition first described by Lewin.¹ It may be due to prolonged use of silver preparations, particularly in hair dyes, or in treating diseased mucous membranes of the eye, throat, and other parts; recently, however, de Schweinitz² and others have directed attention to the danger accompanying long-continued use in this way of the newer silver preparations, such as protargol.

General argyria has also occurred in a few instances from prolonged occupational contact with silver, and, in a smaller number of cases, from its protracted local application. Kobert, indeed, urgently insists that we are likely to enter upon a new era in the history of argyria because of the freedom with which the newer preparations of silver are now being used locally by genito-urinary, ophthalmic, and other surgeons, and, even more, because of the recent frequent use of some of these preparations in comparatively strong solution in the treatment of local disease of the bowel, or intravenously in septic and other conditions. In a great majority of instances, however, argyria has been due to the therapeutic internal use of silver nitrate. In slight degree the condition has been set up by as little as 2 grams (30 grains), administered in the course of two months; but when marked general discoloration occurred, the amount has generally been much larger—15 grams ($\frac{1}{2}$ ounce) or more. The comparatively frequent occurrence of argyria in earlier times, and the very unfortunate results, led to such general and emphatic warnings against the possible production of it that the condition became, and still is, quite uncommon. Many recent graduates in medicine, however, seem to have an insufficient appreciation of the danger. In the past three years the writer has seen 7 cases, 3 of which were of recent origin.

General argyria has occurred through accident; Lewin saw a case as a result of accidental swallowing of a stick of silver nitrate under circumstances that prevented its removal before it was absorbed.

Pathology.—Argyria consists of a deposit of silver, in the skin or mucous membranes alone, in the local form; in the internal organs also, in the general form. In argyria due to internal use of silver, the pigment is found in the papillæ of the skin and in the glands, but not in the epithelium; in occupational cases, in which it enters from the exterior, it may be found in the epidermis. In generalized argyria most of the organs may show pigmentation, but it is ordinarily most marked in the kidneys, liver, and choroid plexus. The pigment is situated in the vessel walls and the nearby tissues. In the early stages it is first found in the leukocytes.

¹ *Berl. klin. Woch.*, 1886, p. 17.

² *Transactions of the American Ophthalmological Society*, 1903.

Silver salts, when absorbed, form an albuminate, and this is gradually deposited and reduced; the reduction occurs through photochemical action in surfaces exposed to light, while in the internal organs it is accomplished by the activity of the cells (Loew).

Chronic interstitial changes in the liver, lungs, and kidneys, have been described as a result of the prolonged presence of the pigment in the tissues.

Symptoms.—The condition consists of a more or less disfiguring pigmentation without any subjective symptoms. Gastric ulcer, chronic nephritis, pulmonary tuberculosis, headache, and weakness of memory, have, without clear justification, been attributed to prolonged use of silver; and an isolated case of neuritis with symptoms resembling the forearm-extensor palsy of lead poisoning is mentioned by Gowers. Marked mental depression and abnormal shyness may naturally result from the very marked disfigurement. As a rule, however, pigmentation is the sole result. When this is due to local application or to occupation, the discoloration begins in the areas that come directly in contact with the silver, and in such it usually remains localized. If it results from internal use of silver, the first pigmentation is almost always seen in the form of a line on the edge of the gum that resembles the lead line, but is of a more violet color. This line is of diagnostic importance and also serves as an important warning, since it appears well before the pigmentation of the skin, and indicates the necessity of stopping the use of silver at once. When skin pigmentation develops from internal use, it is at first in patches, chiefly in areas much exposed to light; the patches afterward coalesce and the whole surface—skin, conjunctiva, and other visible mucous membranes—ultimately shows more or less pigmentation. Slight grades resemble moderate degrees of cyanosis; in more severe cases there is a very striking and characteristic slate-gray color that makes the appearance of the individual extremely conspicuous. The color is often spoken of as resembling the complexion of the Moorish race, but it is really more of a bluish-gray. If distinct pigmentation is allowed to develop while silver is still being administered, the discoloration usually grows more marked after the drug is discontinued, because a considerable amount of unreduced silver is always present in the body under such circumstances, and reduction goes on for some time. The color may indeed continue to deepen slightly for many months; in one case known to the writer it apparently continued to grow darker for years.

Diagnosis.—The discoloration may be mistaken for cyanosis, and the line on the gums may be confused with the lead line. The nature of the condition is determined by the history, or, if desirable, by excising small portions of skin and finding that in sections the pigment granules disappear after treating with potassium cyanide or concentrated nitric acid, and reappear upon adding ammonium sulphide. There is no practical likelihood of mistaking the condition for anything else when the color has once been seen and recognized.

Prognosis.—Once developed, the pigmentation is permanent. If there is merely a line on the gums, disfigurement of the skin may usually be avoided by discontinuing the use of silver at once. If the skin already shows discoloration, this generally deepens somewhat, even if the drug is stopped.

Prophylaxis and Treatment.—The prophylaxis consists in the exercise of great care in prescribing silver nitrate, not giving more than one-fourth grain doses and not continuing it for more than six weeks. If it is desired to use the drug further in the same patient, there should then be an intermission of several weeks. Patients should not be given solutions of silver to use without the supervision of a physician, and they should be warned against the danger of having prescriptions for internal use, or external application, refilled.

There is no treatment for argyria, all practicable methods of combating the pigmentation being entirely unsuccessful.

CHRONIC ZINC, COPPER, BRASS, TIN AND MANGANESE POISONING.

Whether any of these substances produce chronic systemic disease is an unsettled question. There is little doubt that most of them may produce digestive disturbance; and the presence of zinc, copper or tin in preserved foods should therefore be considered prejudicial to health. There is likewise no doubt that the respiratory tract may be damaged by inhalation of dust in the manufacture of any products of these metals. Chronic systemic effects have, however, been but rarely observed, and it has never been clearly shown that the systemic effects described were not due to other unquestionable systemic poisons, particularly lead and arsenic, that are known to be frequently present in the metals under discussion, or to sulphurous and sulphuric acid, carbon monoxide, and other fumes that are given off in the heating of these metals. Characteristic lead poisoning is definitely known to occur occasionally in workers in zinc and copper mines and furnaces, and has been seen as a result of holding brass nails in the mouth. The opinion is now almost general that systemic poisoning, due specifically to zinc and copper, does not occur in those exposed to these metals. Workers in copper, for example, may have so much of this metal in their stomachs that at almost any time a draught of weak sulphuric acid produces vomiting from the copper sulphate formed (Wollner), and they may work in so much dust that, like the employees of the bronze factories at Fürth, they “resemble walking bronze statues”¹ and yet they do not show poisoning. The writer has spent many years in the immediate neighborhood of large zinc mines and furnaces and knows of no zinc poisoning in the men at these works; and Mr. G. G. Convers, of Bethlehem, Pennsylvania, whose opportunities and observations have given him exceptional knowledge in this matter, states that the men who work with the oxide of zinc, which has of course been largely freed from impurities, never show any signs of systemic poisoning even though they spend hours every day in an atmosphere containing much zinc oxide dust. There is also no evidence that drinking-water—which is in some places carried through zinc pipes and in such instances is known to contain frequently considerable amounts of zinc—has caused chronic poisoning. Gimlette attributed digestive disturbance and emaciation to water collected from zinc roofs, but his view was not convincingly

¹ Mayer, *Penzoldt and Stintzing's Handbuch*.

proved even though the water did contain zinc. Kobert has found that zinc workers often excrete large amounts of zinc for months without any evidence of poisoning.

Professor Koenig, who had been much interested in the question of copper poisoning in the employees of the great copper companies in Michigan, has found no evidence of it in them, or in the people who live in the regions about the mines and who drink water that often contains copper. Similar observations have been made by many other writers; and hence even soluble copper salts apparently do not cause chronic poisoning.

Certain chronic local symptoms, however, have been ascribed to these metals. Zinc chloride may produce severe skin irritation through external action; Gimlette considered the epidemic mentioned, in which there was gastro-intestinal disturbance and emaciation, to be due to zinc; and systemic effects such as colic, anæmia, paralyses, and tabetic symptoms have been ascribed to zinc by Schlokow and others. Popoff has attributed similar symptoms to working with bronze, while Schnitzler, Seeligmüller and others have reported neuritis which they considered to be due to copper, but Walton and Carter¹ however themselves suggest that in their cases pressure may have been the actual cause of the symptoms. Suckling reported neuritis in brass workers, and he, Hogben, and Raymond, have described ataxia in brass workers. Murray observed cases in brass workers in which there was colic, anæmia, gastro-intestinal disturbance, emaciation, and even hæmoptysis. Brass workers also occasionally show marked respiratory disturbance and the condition that has been termed "brass workers' ague," in which chills, fever, and sweats occur occasionally and may somewhat resemble malaria. It is not probable that these conditions are produced by the constituents of pure brass.

Copper is known to produce some disfigurement, however, through greenish discoloration of the teeth, the hair, and occasionally the skin of the face and other parts. Even a green color of the sweat has been described. At times other bones than the teeth show this color markedly at necropsy or upon exhuming a body.

The cases of tin poisoning that have been described were probably in most instances intoxication from decomposed canned foods. There are no cases on record that were clearly instances of chronic tin poisoning. Ungar and Bodländer² have, however, produced gastro-intestinal symptoms, heart weakness, emaciation, paralysis, ataxia, and coma, in animals, through subacute and chronic experimental poisoning, and the possibility of chronic poisoning in man must be recognized, for tin is quite extensively employed in weighing fabrics; and tin vessels are, of course, used to an enormous extent in preserving foods, and acid contents of such vessels may contain appreciable amounts of tin. This poisoning must, however, be very rare, if it occurs. It is apparently of little clinical importance (K. B. Lehmann) and we have at any rate practically no definite clinical knowledge of it.

There are no diagnostic signs of any of the poisonings under discussion, as they are not positively known to occur. In cases in which these metals were suspected of producing poisoning, the prognosis seems to

¹ *American Journal of the Medical Sciences*, July, 1892.

² *Zeitsch. f. Hygiene*, Bd. ii.

have been much like that in lead poisoning; and the treatment should follow the same principles.

Chronic manganese poisoning is mentioned separately because, while it has been little studied, it seems, from the observations of Embden, to be perhaps of considerable importance in the limited group of persons who are exposed to it. Embden described a series of cases in which there was œdema, general weakness or pareses without atrophy or degeneration reaction, mask-like appearance of the face, disturbance of speech and of the voice, gross tremor of the head and extremities much increased upon intentional movement, excited patellar reflexes and retropulsion in complex movements and in attempts to walk backward spontaneously. The Romberg sign was absent. There were paræsthesias and pains in the earlier stages but no other sensory symptoms. Sometimes there was uncontrollable laughter, but no other psychic alterations were observed. The condition is not fully recognized as manganese poisoning and needs further study.

CHAPTER VIII.

CARBON MONOXIDE POISONING. ILLUMINATING GAS POISONING. COMBUSTION PRODUCT POISONING. CHRONIC CARBON BISULPHIDE POISONING.

By DAVID L. EDSALL, M.D.,

CONTRARY to the conditions in most of the other intoxications, acute poisoning of the variety now under discussion is of special interest to the medical clinician and neurologist, because it not infrequently produces subacute or chronic disorders. Acute carbon monoxide poisoning is somewhat like acute arsenic poisoning in this respect, since it may be followed immediately or after a considerable interval by more or less persistent conditions that are impossible of correct interpretation unless the previous occurrence of poisoning and its nature are known. It is of more general and more complex interest than arsenic poisoning because of its much greater frequency and because its sequelæ are more varied in nature and often less characteristic. At the present time also, the sources of poisoning are more numerous and more readily encountered by accident or design. Considerable technical knowledge too, is necessary in many instances in order to appreciate the fact that carbon monoxide is the toxic agent; and an added source of confusion lies in the fact that many acute poisonings are suicidal, and unsuccessful attempts at suicide are often subsequently concealed.

It is necessary, therefore, to lay emphasis not only upon those sources of poisoning that act repeatedly or persistently but also upon those that exert their effects through transitory exposure. The acute poisoning with its sequelæ has, indeed, been far better studied than the chronic. The importance of the latter is very difficult to determine, and its clinical picture cannot be very clearly given: this is partly due to the fact that it occurs chiefly in persons whose hygienic circumstances are bad in many ways, and it is hard to determine how large a part carbon monoxide plays in producing any resulting symptoms, partly because it is difficult in many instances to demonstrate that carbon monoxide was present and active at all; partly because the rather small number of investigators who have studied the question clinically have often made partisan statements without due proof, while most of the profession give the subject only casual thought or none.

The forms of poisonings mentioned under this heading are not identical but they are most easily considered together, for the symptoms are similar in all, and carbon monoxide is the chief toxic agent in all. While various gases other than carbon monoxide are present in illuminating gas and in combustion products, and while it has been shown both experimentally and clinically that the effects produced by illuminating gas and combus-

tion products are not wholly the same as those due to pure carbon monoxide, neither the clinical nor the experimental effects of the other gases that are present are sufficiently distinctive to permit of separate description of the three conditions.

Etiology.—Pure carbon monoxide poisoning has been excessively rare because opportunities for its occurrence have been most unusual. It has been seen in a few instances in laboratories, and a number of distinguished investigators have had very grave effects as a result of accident or physiological experiment. In recent years a new cause of almost pure carbon monoxide poisoning has been coming into some prominence. Moissan, originator of the electric furnace for chemical researches, drew attention to the danger of carbon monoxide poisoning if this furnace was used carelessly, and a certain number of cases are likely to appear from this source, because electric furnaces are now so extensively used for commercial purposes. Large numbers of these furnaces have been installed in industries such as those at Niagara Falls, and Mr. F. J. Tone, general manager of one of the companies, states that the furnaces of that company discharge about sixteen tons of carbon monoxide daily, which is as a rule oxidized at once to carbon dioxide and carried off by special ventilating apparatus. He has seen no chronic effects, but states that occasionally the oxidation or ventilation becomes temporarily imperfect and the workmen are quickly made ill, usually with headache, nausea and circulatory failure. The experience in other companies is much the same. Professor Edgar Smith states that two students of chemistry at the University of Pennsylvania had poisoning of moderate severity from this source, which left mild mental symptoms for weeks afterward.

Intoxication with illuminating gas is commonly looked upon as being practically carbon monoxide poisoning, but Ferchland and Vahlen's experiments¹ show that illuminating gas really produces a more severe poisoning than does simple carbon monoxide; nevertheless carbon monoxide is certainly the chief agent in the poisoning. Water gas, as is well known, is particularly dangerous because of the large amount of carbon monoxide that it contains. Acute cases of gas poisoning are, of course, usually due to leaving the gas turned on in sleeping rooms, either by accident or attempt at suicide; in the last-mentioned connection, this poisoning has a profound economic importance because more deaths are at present due to this cause than to any other form of suicide by poisoning. Intoxication with illuminating gas sometimes occurs in the acute or chronic form in employees of gas works; and protracted poisonings of slight degree, occasionally acute and even fatal cases, may occur in the occupants of buildings from which gas escapes from leaks in the pipes or fixtures. Pettenkofer and others have shown that the leak need not be in the building itself; the gas may travel through the ground for some distance, certainly for many yards, and hence while escaping from the mains may reach the interior of houses that are at a considerable distance from the break. This is especially likely to occur in winter, when the heating of the interior of buildings causes active motion of the atmosphere, and thereby draws the gas into houses by aspiration. This manner of poisoning at long range, so to speak, is not confined to illuminating gas; it has

¹ *Archiv. für exper. Path. und Pharm.*, Bd. xlviii, Hefte 1 and 2.

occurred from mines situated near dwelling houses. It is also of importance and much interest that under these circumstances the odor of the gas is usually lost, and hence its presence may be detected only through the occurrence of poisoning. Intoxication from this source is probably quite uncommon now, however.

The exact frequency and importance of chronic illuminating gas poisoning is not well known, and it is hard to determine because of technical difficulties in the study of the question. It is probably of somewhat greater consequence than is generally recognized, but is almost certainly less important than it has been thought to be by many who have written of it since Pettenkofer's studies were published.

Combustion products cause poisoning chiefly as a result of the carbon monoxide they contain, though this is intensified by the other gases present, more particularly carbon dioxide. The amount of carbon monoxide in such gases naturally varies greatly, but it may be exceedingly large. In iron furnaces, for example, the escaping gas may contain as much as twenty-five per cent. to thirty per cent. Mild grades of combustion product poisoning very frequently occur and severe cases are not extremely uncommon. Nearly every one has experienced transitory effects from gases produced by heating apparatus with poor draughts, and such mild effects are common in persons who are closely confined in rooms heated by badly drawing stoves or house furnaces. More or less severe effects also occur at times in cooks, and in persons employed in charcoal furnaces, iron and similar furnaces, in coke ovens, in gas plants, in tar distilleries, in the moulding of various metals, in kilns of various kinds (brick, tile, pottery, etc.) and in similar occupations.

The "miner's disease" that has aroused so much interest, has been shown to be due chiefly to carbon monoxide derived principally from the explosive used in blasting. Carbon monoxide poisoning also occurs at times in the employees of chemical factories. In the various occupations mentioned, severe and even fatal acute poisoning is sometimes seen, and chronic ill health occurs not infrequently.

The cases that occur accidentally in households are usually mild but are sometimes very severe; as in several instances in which one or more members of a household suffered from poisoning that was so pronounced as to produce unconsciousness, and in which severe after-effects occurred, a stove or house furnace being the cause. Fatal cases have occasionally occurred even from modern heating appliances; in some European places, this is considered of such importance that the use of dampers in stove pipes is not permitted. When charcoal braziers, and other fires without chimney connections were much used, domestic poisoning of all grades of severity was quite common, and the brazier, as is well known, has often provided the means of committing suicide. Cases are still occasionally reported from the use of such heat in apparatus for drying out excavations, etc. A few years ago a number of severe and even fatal cases were caused by the cab heaters in Paris, Gautier himself having suffered severely. Recently the common use of gas or oil stoves in small and ill-ventilated rooms, and particularly the use of gas water heaters in bathrooms, has led to a noteworthy number of poisonings, some of which have been very severe; one of the nurses at St. Christopher's Hospital, Philadelphia, had prolonged and nearly fatal coma from this cause.

Pathology.—The lesions have been studied with reliable results almost solely in acute cases or in those that die while suffering from sequelæ of acute poisoning. The striking features in acute cases are the red or bluish-red spots on the surface of the body, chiefly the front of the neck, trunk and thighs; the brilliant cherry-red color of the blood and of many or all the organs; the marked degenerative changes in the muscles; the scattered, small hemorrhages and intense hyperæmia of all the organs; and in many cases marked cerebral changes. Among the immediate or more remote sequelæ are gastro-enteritis, sometimes pseudomembrane formation on the upper digestive and respiratory passages, bronchitis, bronchopneumonia, or at times lobar pneumonia. Nephritis is common, sometimes with very severe degenerative changes and interstitial reaction. Peripheral neuritis has repeatedly been described, and poliomyelitis and disseminated encephalomyelitis have been seen. The most important nervous lesions, however, are those in the brain: they are chiefly hyperæmia; scattered, small hemorrhages, with occasionally more extensive hemorrhage; and striking foci of softening, which particularly tend to be situated in the lenticular nucleus and the internal capsule, but may involve various parts of the basal ganglia. Cysts may form as a result of the softening. The areas of softening have a striking tendency to be symmetrical; they are probably the result of primary changes in the vessels, though there is some evidence that both the softening and the diffuse changes in the cells of the cortex and in the nerve fibers, that are often seen, are due to a primary encephalitis. Sibelius has recently discussed the literature relating to cerebral symptoms and lesions.

In chronic poisoning Koren has described fatty changes in the vessels and heart, with cardiac dilatation, anæmia, splenic enlargement, and pleural effusions.

Mode of Entrance and Pathogenesis.—Carbon monoxide enters the system solely by inspiration, unless experimentally introduced otherwise. Its chief effect is in displacing the oxygen from oxyhæmoglobin and forming carbon monoxide hæmoglobin, thus rendering the affected portion of the red blood corpuscles incapable of performing their function as oxygen and carbon dioxide carriers. This combination is commonly spoken of as a permanently fixed one; it is relatively fixed, but not absolutely so. Oxygen cannot directly displace the carbon monoxide from its hæmoglobin combination and it is not probable even that any noteworthy amount of the carbon monoxide that is thus combined, is oxidized to carbon dioxide and excreted in this way; but it has been established that dissociation of carbon monoxide hæmoglobin occurs, and also that carbon monoxide is excreted as such, in the expired air, after poisoning. Detoxication is, therefore, always carried out to some degree and small repeated doses are probably rapidly excreted in this way. There is no evidence that it is gotten rid of by actual destruction of the affected corpuscles. Fodor has claimed that carbon monoxide has a cumulative action when taken in small doses, but there is no good proof of this.

It is not yet fully settled whether the gas has any direct toxic action upon animal tissues or whether it acts solely by robbing the blood of its effective hæmoglobin, but it is highly probable that both occur. The testimony differs as to whether it poisons animals whose blood contains no hæmoglobin, bacteria, and the higher forms of plants; but a number

of experimenters consider with much reason that it has a direct toxic effect, in higher animals at any rate, exerting this chiefly upon the central nervous system, the muscles, the nervous mechanism of the heart, and some other organs, and also upon the peripheral nerves and the parenchyma of various organs.

An atmosphere becomes dangerous when it contains 0.05 per cent. of carbon monoxide (Gruber, Haldane). Severe symptoms may be caused by 0.02 per cent. (Haldane). Fodor has shown the presence of carbon monoxide in the blood of animals that had breathed an atmosphere containing only one part in 25,000, but such amounts are not positively known to cause any ill effects. This whole subject has recently been extensively reviewed by W. Sachs.¹

Symptoms.—The main symptoms of acute poisoning are an indefinite feeling of illness, usually accompanied by throbbing of the vessels, a burning sensation in the face, and soon by severe headache, vertigo, and very marked muscular weakness, the latter being a somewhat characteristic and peculiar symptom. Nausea and vomiting often occur. If the dose is large, severe symptoms develop; the subject becomes drowsy and then loses consciousness, and with this, there is usually loss of control over the sphincters. Sometimes unconsciousness comes rather gradually, sometimes, as occasionally with miners, for example, it may be the first symptom, and the subject may drop as suddenly as if he had been shot. Muscular twitching is common, even in the earlier stages, and sometimes convulsions occur when the symptoms have become more marked. Very commonly the patient is not seen until he is unconscious, when he shows heavy and unduly rapid breathing, the pulse is sometimes fairly full and strong but generally very rapid, and it is weak if the poisoning is severe or advanced. The skin and mucous membranes are usually more or less cyanotic, but this is sometimes made obscure by a peculiar and characteristic redness of the skin. There are, at times, the red patches on the skin mentioned under pathology. Drawn blood is bright cherry-red in color and gives the characteristic reactions for carbon monoxide. If recovery occurs, there is a gradual awakening, and for some hours, often much longer, a hazy mental state persists. Coma may last many days and then be followed by recovery. Gilman Thompson,² considers it a bad sign if the leukocytosis, which is usually present, is of high degree.

The sequelæ are common and interesting. There may be nothing but weakness and fever; these usually occur in some degree and last for variable periods, it may be for only a day, or even for several weeks particularly when pulmonary sequelæ develop. The fever is frequently associated with bronchopneumonia, much less commonly with lobar pneumonia, but sometimes no cause for it is evident. This fever has caused interesting errors in diagnosis, particularly in accidental cases, and especially when the poisoning has been prolonged, but not severe enough to cause violent cerebral manifestations at the onset. House epidemics that were very puzzling and in which the cause was traced with great difficulty, have occurred and have repeatedly suggested infections; cases have been considered to be typhoid fever, for example, because of the fever and "typhoid state." Pulmonary sequelæ as indicated

¹ *Die Kohlenoxydvergiftung*, etc.

² *Medical Record*, July 9, 1904.

are very common. Bronchitis, bronchopneumonia, rarely lobar pneumonia, occur and are of extremely variable duration, sometimes causing death weeks after the poisoning. The vascular system shows marked involvement during the acute attacks, and localized hyperæmias, cardiac palpitation, and irregularity often occur for indefinite periods afterward. Gastro-intestinal disturbance is not uncommon and may persist for a long time; gastric irritability, tenderness and pain of long duration have been repeatedly described. Icterus has been seen in rare instances. A striking and very common symptom of the poisoning, which is a sequel also, though a transitory one, is glycosuria. Skin lesions are common; local necroses and gangrene in areas exposed to pressure occur frequently, and heal slowly, and vesicular, herpetic, and bullous lesions have often been seen and they also heal poorly. Localized œdema (Klebs) or gelatinous infiltration (Litten) and curious areas of redness and swelling, that may closely resemble cellulitis, have occurred.

The most important sequelæ involve the nervous system. Neuritis, usually localized, with paralysis and anæsthesia, neuralgias, choreiform movements, intention tremor, scanning or stuttering speech, and incontinence of urine have been seen alone or associated with other symptoms. Cases with symptoms of Landry's paralysis or of distinct multiple sclerosis have been described. Ocular disorders are not very common but are extremely interesting; there may be partial or complete blindness of varying duration, with or without ophthalmoscopic changes, xanthopsia, nystagmus, and paralyzes of the eye muscles, and there have been repeated instances of complete ophthalmoplegia with marked protrusion of the eyeballs. Occasionally, deafness or roaring noises in the ears develop. Persistent headache sometimes follows. The most common and the gravest nervous sequelæ are those due to cerebral changes; these may be local or diffuse and the results are chiefly paralyzes or mental disturbances. These disorders tend to occur chiefly in those well advanced in life, but have been seen even in a five year old child; they may develop a considerable time after the poisoning. The paralyzes from this cause are, of course, likely to persist; they may be monoplegic or hemiplegic. The mental disturbances vary much in type; they include simple hallucinations, simple confusion of more or less pronounced degree, very remarkable instances of amnesia, mania; but most commonly, the mental disturbances are confusional states or, in persistent cases, actual dementia.

It is of very great importance to keep in mind the fact that sequelæ of all kinds may appear immediately after the poisoning, or may be postponed for weeks; blindness, paralyzes, mental disturbances and other sequelæ have repeatedly been seen days or weeks after the poisoning, and the cerebral changes have a strong tendency to be delayed in their appearance. It is of equal importance to note that sequelæ often of much gravity may be caused by a mild attack of poisoning. Cheneau, in his investigations, was very moderately poisoned but had distinct mental and physical symptoms for months afterward, and Professor Smith's students had in both instances weeks of disturbance, which in the one case was a "far away" mental feeling, in the other marked depression.

The symptoms of chronic poisoning have not been satisfactorily studied. They differ qualitatively as well as quantitatively from those seen in acute cases. There are complaints of headache, vertigo, nausea

and sometimes vomiting. Often there is slow pulse and usually, there is general weakness, languor, and anæmia; very recently, however, Reinhold has described two interesting cases in which there was a pronounced polycythæmia with over 11,000,000 red cells. With the above mentioned symptoms, there is usually some mental disturbance, lack of concentration, sluggish intellectual action or poor memory. These symptoms tend to increase, and may be associated with weak or absent tendon and pupillary reflexes; Musso described a series of 5 patients, 2 of whom recovered after nine months, while the other 3 became demented and died with the typical picture of parietic dementia. This subject is one that deserves much more general attention and study, particularly in relation to poisoning from combustion products.

Diagnosis.—This depends upon the history, a knowledge of the technique of the patient's occupation, or demonstration of the presence of carbon monoxide in the blood. The best tests for the latter are Hoppe-Seyler's sodium hydrate test or his spectroscopic test; Katagama's reaction; or the Kunkel-Welzer reaction with potassium ferrocyanide and acetic acid. The sodium hydrate test is made with a solution of about 1.30 specific gravity; add this to the blood, and with carbon monoxide poisoning the result is a clotted mass of bright-red color, while normal blood gives a mucoid-like mass of greenish-brown color. The spectroscopic test depends upon the fact that carbon monoxide hæmoglobin is not reduced by such substances as ammonium sulphide. Oxyhæmoglobin and carbon monoxide hæmoglobin produce two absorption bands that are much alike, the chief difference being that the carbon monoxide hæmoglobin bands are somewhat nearer the violet end of the spectrum. If, however, ammonium sulphide is added, normal blood shows the single band of reduced hæmoglobin, though this often becomes accompanied soon after by the hæmatin band; ammonium sulphide, on the contrary, does not affect the carbon monoxide hæmoglobin spectrum, and the absorption bands therefore remain as before. With some care they can be easily distinguished from the two bands due to reduced hæmoglobin and hæmatin, for the hæmatin band lies in the red, while the carbon monoxide bands are both in the yellow. Katagama's test consists in adding to 10 c.c. of blood diluted with water 0.2 c.c. of ammonium sulphide solution and 0.2 c.c. of 30 per cent. acetic acid. Carbon monoxide blood gives a bright-red precipitate, normal blood a greenish precipitate. In the Kunkel-Welzer test, undiluted blood is used and an equal amount of 20 per cent. potassium ferrocyanide and a small quantity of 30 per cent. acetic acid are added; carbon monoxide blood gives a bright-red color, normal blood blackish-brown; the difference may persist for weeks. Tests may be made with copper salts, lead acetate, etc.; the precipitate that they produce with carbon monoxide blood is bright red while with normal blood it is a dirty dark-brown color.

These tests in doubtful acute attacks will occasionally clear up the nature of subsequent sequelæ. Two years ago, for example, a patient in the care of the author had for over six weeks insanity of confusional type associated with marked hallucinations, and ending in paralysis and death; the nature of the case would have been very obscure had it not been determined by chemical tests when he was admitted, at which time he was comatose.

The poisoning should be easily recognized if the history is clear, but may readily be misinterpreted if the source is not known. Acute attacks are likely to be mistaken for alcoholism or uræmia. Among the points distinguishing them from the former, are the absence of odor of alcohol, the marked hyperæmia of the surface and the chemical tests. Uræmia is distinguished chiefly by the urinary conditions and the cardiovascular changes, together with the history and the absence of carbon monoxide, if tested for. Chronic cases are very difficult of proper interpretation. Pettenkofer insists upon the importance of looking for this cause of poisoning, if various persons in the same house have a tendency to wake with headache or nausea. Proper consideration of the occupation will often lead to a correct diagnosis of chronic cases. The reliability and delicacy of chemical tests of either the blood or the respired atmosphere in chronic cases are not very certain as yet, and these have not so far been made very valuable to clinicians.

Prognosis.—In acute cases, this depends largely upon the dose, but much more upon the rapidity with which treatment is undertaken. Patients usually recover if they are promptly and energetically treated; in the last five years, there have been received in the Episcopal Hospital, Philadelphia, 39 cases; of these, 34 recovered; and of the fatal cases several were due to sequelæ. Even with recovery from acute symptoms, the prognosis should be a little guarded for at least a month or six weeks, until it is determined that sequelæ are not about to follow, for some of the most serious after-effects have ensued upon mild poisoning. If sequelæ occur, their prognosis must be determined by the individual circumstances; naturally, those due to central nervous lesions are especially unfavorable. Sequelæ are more likely to occur in persons of advanced years, particularly the cerebral ones. The chronic poisonings are of good prognosis if they have not caused distinct mental changes. In the latter case it must be guarded.

Treatment.—The treatment of acute poisoning consists in immediate removal from the poisoned atmosphere, free use of oxygen inhalations, venesection followed by intravenous or hypodermic administration of normal salt solution, artificial respiration if necessary, and the generous exhibition of stimulants (caffeine, digitalis, strychnia) if they are required. Persistent treatment suffices to bring most cases out of even the most desperate straits. In chronic cases, the removal of the cause is of chief importance, with subsequent treatment of the anæmia or other features. This condition is deserving of greater attention from the standpoint of prophylaxis, particularly in the dwellings and workrooms of the poor, who often have ill-constructed heating apparatus, and who husband warmth at the expense of breathing bad air. The general public also needs to have a better appreciation of the occasional danger attendant upon the use of gas and kerosene stoves and water heaters. The prophylaxis of chronic occupational poisoning is dependent chiefly upon hygienic construction and management.

CHRONIC CARBON BISULPHIDE POISONING.

Chronic intoxication with carbon bisulphide has never received much attention in America, and the number of cases that occur is also much smaller than it was, both because of hygienic improvements and because local conditions of trade in this country have led to a great reduction in its use here in the manufacture of rubber goods. Other substances have to a large extent replaced it in the manufacture of rubber clothes especially. Carbon bisulphide is to a certain extent still used in making the cheaper grades of rubber clothes and also some other rubber articles, especially those that are not intended for long service; for example, it is pretty generally used in the manufacture of surgeon's rubber gloves. Hence, although this form of poisoning is rare, it occasionally occurs; and it is probable, as Laudenheimer states, that a very considerable proportion of the cases that do appear are misinterpreted. There are several reasons for the latter statement. In the first place the cases reported have come chiefly from a relatively small number of specially interested observers, while the industries that may cause poisoning are much more widespread, and hence it is probable that there is but a limited appreciation of the fact that carbon bisulphide is freely used in certain industries and that it produces poisoning in those employed. A second important reason is that the clinical picture of the poisoning is extremely varied and there are no symptoms that directly indicate the nature of the intoxication, knowledge that exposure has occurred being necessary in order to establish a diagnosis, and usually even to suggest it.

Etiology.—Intoxication with this substance occurs almost entirely as an occupational condition. Acute poisoning has occasionally occurred from swallowing large amounts for suicidal purposes or by mistake, and accidental intoxication through inhalation has been described, but in most acute and practically all chronic cases occupation is the source. Carbon bisulphide is used chiefly as a solvent for sulphur and various fatty substances. The industry in which most of the reported cases of poisoning have occurred is the making of various forms of rubber goods, vulcanizing having for more than half a century been done with a solution of sulphur in carbon bisulphide. In the beginning of the latter half of the last century, when the substance came into use for this purpose, the vats containing it were freely exposed in rooms that had poor natural ventilation and no special ventilating apparatus; and at that time Delpech, who made the earliest and a very thorough and extensive investigation of this form of poisoning, found the health of the workmen so frequently and so seriously affected, that governmental action to control the use of carbon bisulphide was soon taken. Since then, comparatively few cases have been reported from France. In more recent times many cases have occurred in England and Germany, Laudenheimer having reported over 50 cases in Leipsic within thirteen years. The gravity of the danger when these industries are practically uncontrolled is illustrated by the fact that vulcanizing "had increased at least tenfold in fifteen years" in and about Leipsic, and yet at most 250 persons were employed as vulcanizers; nevertheless over 50 cases of severe poisoning had occurred in this small group of persons within thirteen years, and from one factory

where only 10 persons did vulcanizing, 6 cases of psychosis were sent to the Leipsic Psychiatric Clinic in the period 1885-87. Rebuilding and instituting hygienic arrangements in this factory were so effectual that no cases were received from it in the ensuing four years. In this country carbon bisulphide is probably not used extensively in more than half a dozen rubber factories. In one of these, where the ventilating apparatus is excellent, they still have an occasional case of poisoning, especially of transitory acute intoxication in new workmen; in some others they state frankly that no precautions against poisoning are taken, and the workmen employed in them must therefore be dangerously exposed.

Other occupations have caused intoxication in unusual instances. Chemists, for example, use carbon bisulphide and in certain lines of work employ it freely and frequently, and this has caused even grave chronic poisoning; but the exposure of chemists is, as a rule, so slight and so brief that serious results are very rare. It is used to some extent in extracting fats from wools, in purifying paraffin and oils, in dissolving asphalt, in extracting sulphur from some ores and in separating crystalline from amorphous sulphur, in extracting fats from seeds, in extracting vegetable perfumes, in freeing bones from fat, in making collodion, in removing varnish, and in various other ways, even in exterminating prairie dogs and rabbits. In most of these the manner of use makes the danger of poisoning slight. Serious danger may, however, occasionally be found in new and unexpected sources. Recently a factory producing so-called "artificial silk" has furnished a number of cases at the University Hospital in Philadelphia.

Pathology.—The lesions in the condition have been little studied in human beings. Schwalbe, Kiener and Engel, and Poincaré have investigated the effects on animals, and Köster has recently reported the most complete and suggestive experimental research that has yet been made. Beyond some emaciation, definite and constant effects do not seem to occur except in the nervous system. Pigmentation of various organs was noted by Schwalbe and by Kiener and Engel, but Köster searched for it with negative results. Changes in the red blood corpuscles have also been observed but are not constant. The same is true of methæmoglobinuria (Westberg); various observers have found it absent. In human cases any noteworthy blood changes are not usually found. The cause of death in acute poisoning seems to be respiratory paralysis and asphyxia (Levin, Köster), and any blood changes seen in chronic cases are probably due largely to mild chronic carbon dioxide poisoning. The nervous system suffers severely, however, and Köster considers the changes he found to be somewhat specific. He observed degenerative changes in the medullary sheaths throughout the nervous system, but less marked in the nerve roots and peripheral nerves than in the central nervous system; the myelin was fragmented and along the course of the nerve fibers and near them were large round or oval objects and also numerous granules, both of which took fat stains; the nerves also showed swelling and irregularity of outline and oedema; and the ganglion cells showed several striking forms of change. In the ganglion cells fatty degeneration was common, and it frequently began in the dendrites or in localized portions of the cell body; the nucleus frequently became involved, though later than the cell body; the pericellular spaces were frequently widened; the end

branches were often broken off. Quensel has recently reported a fatal human case in which there were extensive changes in the central nervous system but none that are not often found in other conditions.

Mode of Entrance and Pathogenesis.—As stated, inhalation is the usual mode of entrance, but there is some distinct clinical and experimental evidence that purely local changes (anaesthesia, paraesthesia, neuritis) may be produced by frequently dipping an extremity into carbon bisulphide. The way in which the poison acts is not wholly clear but it seems certainly to have a special affinity for the central nervous tissue, and from what is generally known about it one would suspect a solvent action upon the lipid elements of this tissue. Acute human or experimental poisoning, except that convulsions often occur, resembles that due to alcohol or to the anaesthetics in that it produces excitement followed by narcosis, and in chronic cases the effects may resemble chronic alcoholism; but the actual chemical action has not been determined.

The amount of poisoning necessary to produce symptoms has been studied by Rosenblatt and Hertel. They find an hour's exposure to 2.07 mg. per liter of air (Rosenblatt), or even to 1.1 mg. per liter (Hertel), sufficient to cause symptoms; when seven or eight hours' work must be done, an atmosphere containing 0.5 to 0.8 mg. (Rosenblatt), or (according to Hertel) 0.8 to 0.9 mg., per liter may cause poisoning. Carbon bisulphide is soon eliminated, a day or two usually sufficing for the excretion of even large doses.

Symptoms.—Some emaciation is common; nausea or vomiting and constipation may occur early; eczema is sometimes observed; strangury has been noted; and disturbance of the sexual function is a very common feature, particularly in more advanced cases with marked psychic or spinal symptoms, but sometimes even when other severe nervous symptoms are absent. The earlier stages of poisoning are often associated with sexual excitement, while in the late stages, especially when severe nervous symptoms of other form have developed, sexual power is usually reduced or lost. Nocturnal emissions or involuntary seminal discharges also appear to occur frequently. Women show menstrual anomalies, and if they become pregnant abortion or miscarriage is likely to occur.

Headache, which may be very severe, vertigo, palpitation, frightful dreams, insomnia, mental depression, and apprehension without distinct psychosis, may be present in the earlier stages, and the English Committee that investigated this poisoning especially insisted upon the frequency of visual disturbances even in very early stages.

When clearly recognizable intoxication occurs, however, it presents the picture of organic disease of the nervous system with or without psychosis, or it resembles hysteria more or less closely, or organic and "hysterical" symptoms are combined. The grouping of symptoms appears to be of almost endless variety. The common presence of so-called hysterical symptoms, especially of anaesthesias of the hysterical type, usually combined with symptoms of actual organic lesions, is one of the most striking characteristics. A much graver and hence more important feature is the tendency to pronounced and sometimes incurable psychoses. The symptoms of a spinal lesion, particularly symptoms of tabetic type are also often present.

The important details are the following. Anæsthesia is extremely common. It may be limited to the area of distribution of one or more nerves and may be associated with other signs of mononeuritis or polyneuritis, though actual evidences of neuritis are apparently very uncommon, in spite of the earlier statements of the French School. Much more frequently the anæsthesia is glove-like, affecting the hands or feet or both, and having no relation to nerve distribution; Delpech thought the hands were more frequently anæsthetic or parietic in those whose occupation caused the hands to be much exposed to the vapor or fluid, and some other authors have agreed with him, while still others have questioned this. Not infrequently there is hemianæsthesia, diffuse anæsthesia, or local areas of distinctly hysterical type. Delayed sensation may be seen. Paresthesias of various kinds and of varied distribution also occur; a common complaint is a feeling of coldness, especially of the hands, and the extremities may actually be very cold, perhaps as a result of local action of the poison. Hyperæsthesia occurs, particularly in the feet, or more commonly in the ovarian region, in cases with hysterical symptoms. The nerve trunks have occasionally been found tender, Delpech having repeatedly noted this, and Laudenheimer having seen it in cases in which there was also paralysis of the peronei and therefore, perhaps, neuritis. Spontaneous pain, especially along the course of nerves, is sometimes quite marked (Delpech, Rosenblatt, Hertel).

The special senses are frequently affected, particularly vision and taste. Ring vision, macropsia, micropsia, obscuration of vision, chromatopsia, *muscæ volitantes*, and other disturbances may be present with or without signs of organic lesion. Amblyopia is extremely common even early in the poisoning. A persistent taste of carbon bisulphide long after the poison must have been completely excreted is a common complaint, or everything may taste sweet or bitter. In their experiments Rosenblatt and Hertel noted first a salty and then a bitter taste. Disturbances of smell, especially a constant odor of carbon bisulphide, have been repeatedly observed. Delpech and others have noted more or less pronounced unilateral or bilateral deafness or roaring noises in the ears.

The reflexes, both superficial and deep, may be normal, excited, reduced, or lost. The cremasteric reflex is often absent, particularly when sexual power is lost. The knee-jerk shows various changes; the fact that it may be absent is a point of much importance in the pseudotabetic cases, as is also the fact that the pupillary reflex may show any variety of change. There may be also disturbance of the sphincters of the bladder, and loss of sexual power. If ataxia is joined to some or all of these symptoms, *tabes dorsalis* is extremely closely simulated.

Motor symptoms are very common. Tremor is occasionally observed; Laudenheimer states that it is almost constant in the maniacal form of psychosis, and in other cases it is at times associated with symptoms that produce a resemblance to general paresis or to chronic alcoholism. Tremor has been seen in such violent form that it greatly or completely interfered with the patient's work. Ataxia is often present; Köster holds that the ataxia and the common weakness of the peroneal muscles produce a peculiar and characteristic gait with a combination of steppage, ataxia, and shuffling.

The most important motor symptom is paresis or paralysis, paresis being the much more common. In severe form it is most frequent in the peroneal muscles, and the especially common involvement of the lower extremities has led many to the view that the poison acts upon them locally, since the vapor is heavy and tends to sink to the lower levels of the workrooms. This idea is, however, pretty well disproved by the fact that in animal experiment the hind legs are especially affected, even though all the extremities are equally exposed. The paresis also frequently involves the hands and arms, and a feeling of general weakness is a common, indeed an almost constant complaint, even in the early stages of poisoning. This weakness may be of the most extreme severity so that the patient may become unable even to feed himself. Paresis may be of one extremity alone, or of both legs or arms or of half of the body; and the actual paralysis that occasionally appears may have a similar distribution, producing monoplegia, hemiplegia, or, more commonly, paraplegia.

Muscular irritability is often increased in early stages, and there may be cramps and local spasms of the facial, the orbicularis, and other muscles. A pseudotetanic condition has been described by Rendu. General convulsions are a peculiar feature of acute poisoning as contrasted with other narcotic intoxications, and they may occur in severe chronic poisoning and may even become persistent (Laudenheimer). Contractures may follow paralyses. Atrophy is not infrequent in the cases with paresis of the extremities; it involves chiefly the interossei and the peroneal muscles. It is likely to be associated with loss of faradic irritability and degeneration reaction; and a point of much interest in relation to the more or less profound weakness of the extremities, so common both early and late, is that poisoned animals showed pronounced fatigue reaction (Köster).

Psychic disturbances are common and very important. Their character varies greatly. Transitory attacks often occur in which there are hilarity and general exaltation resembling acute alcoholism; less commonly there is depression. If the exposure continues, these attacks occur repeatedly and more readily, and a more or less prolonged psychosis may develop. Symptoms of a definite psychosis usually appear rather suddenly, and most commonly in persons who have a hereditary predisposition. As a rule they develop after but a few weeks' exposure, while other severe nervous symptoms (spinal or hysterical) are not likely to occur unless the exposure has been prolonged. Laudenheimer divides the psychoses into three general groups; while the psychic symptoms are so variable that it is doubtful whether any classification can be well adhered to, this grouping serves to make somewhat clearer a description of the characters that the cases are likely to present. He describes a maniacal, a depressive, and a stuporous form. The first is important in that the prognosis is almost always good; it usually occurs in persons with a good family history; it develops suddenly; and the chief feature is motor and intellectual excitement, usually hilarity. Erotism is common; hallucinations rarely occur. Hypochondriacal complaints constitute an odd but frequent feature, and tremor is almost constant. The pupils are usually unequal or react slowly. The duration is rather short, usually one to four months.

The depressive form is of much worse prognosis; four of Laudenheimer's ten cases persisted. This form exhibits marked hallucinatory

delusions and excitement, with profound apprehension and severe hypochondriasis. The favorable cases average three and three-quarters months' duration. Simple melancholia, Laudenheimer has never seen. The stuporous form may be acute and rapidly improve, or may persist. This form shows no motor excitement. The pupils are dilated and react slowly. Other varied psychic disturbances also occur, and the individual cases do not readily come within distinctive groups.

The symptoms of hysterical character in this poisoning are of great interest in themselves, and also of special interest because they have been used by some authors, particularly of the French School, in favor of the view that hysteria is due to some essential anomaly in the individual and is merely brought out by any "provocative agent" such as carbon bisulphide, and is not due to any direct effects of such agents. It has even been claimed by Marie and others that carbon bisulphide poisoning is essentially hysteria. Köster, however, has shown that anaesthesia of characteristically hysterical distribution was produced in a large proportion of the animals poisoned with carbon bisulphide, a sufficient evidence that the anaesthesia need not be "hysterical," even though its distribution is of this type. As has been noted, hysterical signs are often combined with those of chronic disease. The latter signs may be of the most mixed and illogical character, but in such cases organic disease is usually present, and the anaesthesias even, though of hysterical type, are probably due to organic lesions. In other cases careful search for distinct signs of organic disease has apparently shown their absence, and there are only functional symptoms, such as profound weakness, visual and gastric disturbance, and hypochondriasis, together with stigmatic anaesthesia. The interpretation of these cases is difficult, but it seems to me that Köster makes good his contention that there is no definite place to draw a dividing line, and these should be provisionally considered to be actual organic carbon bisulphide poisoning rather than essential hysteria in which carbon bisulphide is a mere collateral provocative agent.

Diagnosis.—This depends upon a knowledge of exposure to carbon bisulphide. The only characteristic features of the symptoms are their extremely varied character and the apparently illogical manner in which they are often combined, and these are manifestly insufficient for a diagnosis if there is not a good suspicion at least of exposure. The distinction from psychic, spinal, ocular, and hysterical disorders of other source will depend upon demonstration of exposure; the exclusion of tabes dorsalis, for example, may depend almost absolutely upon this, so closely may it be simulated. Occasionally other central nervous lesions will be extremely closely simulated; sometimes neuritis is present, in which case the cause may easily be overlooked; more often neuritis will be simulated by central lesions.

The determination of the character of the lesion present demands careful study of the symptoms. Peripheral neuritis was accepted as present in many cases by the French School, particularly in the pseudotabetic cases, but more accurate observation almost always demonstrates signs of central disease in such cases. Hysteria is very likely to be diagnosed in a considerable proportion of cases, but more careful study will frequently show evidences of organic lesion; and even when these evidences

are absent it is not justifiable, in this poisoning at any rate, to consider hysterical symptoms entirely functional.

Prognosis.—Mild transitory attacks of psychic or other disturbances are not likely to be followed by any permanent results unless exposure continues; when the exposure does continue and repeated transitory attacks of intoxication occur there is serious danger of a grave psychosis. The outlook in these cases has been already indicated. The cases with spinal symptoms and those with peripheral symptoms usually recover slowly, but if they have lasted for a long time and the symptoms are very severe there may be little or no improvement. The general depression of health and the hysterical symptoms, muscular weakness, etc., appear to last for a long time. The eye symptoms are of much importance. They often recover but the English Ophthalmological Society found that about 20 per cent. showed no improvement and about 25 per cent. more showed imperfect recovery. Recurrence of any symptoms from which the patient has recovered or the development of new symptoms is extremely probable if he returns to work in which he is exposed.

Prophylaxis and Treatment.—Prophylaxis should be of very specific character. Treatment is almost entirely symptomatic. Workmen should wear gloves and use instruments for dipping the material into the carbon bisulphide mixture instead of exposing their hands, and they should also be taught extreme care about exposing themselves to inhalation of the vapor. All these will be of relatively little avail, however, unless proper ventilation is secured by means of special apparatus and the rooms are so constructed that proper ventilation can be carried out. If these things are done most of the cases can be avoided. When the poisoning has developed, treatment is largely a question of absolute removal from exposure, symptomatic drug treatment when necessary, and the use of the general eliminative measures indicated in any intoxication. Phosphorus was at one time used freely by the French School, they believed with good results; but apparently it is no longer used, and there is no drug that has any peculiar value. Oxygen inhalations have been recommended but are probably of little use. The most important points are, unquestionably, fresh air; passive or, if possible, moderately active exercise; and seeing to it that the excretion from the intestines and kidneys is satisfactory. Alcohol should be rigidly excluded, as should sexual and other excesses.

PART IV.

DISEASES CAUSED BY ORGANIC AGENTS.

CHAPTER IX.

ALCOHOL.

By ALEXANDER LAMBERT, M.D.

Historical.—From time immemorial man has used some substances to help increase the joys of life or deaden the keen edge of sorrow. Alcohol in some form has probably been most extensively employed for these purposes and, whenever used, it has been to excess. The monuments of the Egyptians show the use and abuse of wine; the oldest Chinese manuscripts contain records of drunkenness; and in the Vedas there are prayers to the Deity beseeching Him to condescend to come and get drunk with his worshippers, that he might grant their requests and bestow favors upon them which, when sober, he would refuse. The Old Testament contains records of its widespread use, of consequent drunkenness, and warnings against the evils which follow alcoholic excess. As civilization developed, man learned to make liquids containing a higher content of alcohol and the civilized races have taught the uncivilized to substitute the distilled for the weaker fermented liquids. Acute and chronic alcoholism have been present from the unknowable past to the present day, and their occurrence has always been bound up in the routine of man's daily toil, in the expression of his emotions, and in the performance of his religious rites.

Etiology.—An unstable nervous system is the fundamental basis on which habitual alcoholic excesses develop. There is the weakness of will, the tendency to over-indulgence, the lack of self-control, and when once the narcotic effect of alcohol is felt, the inevitable craving for more cannot be resisted. In these weak individuals there is often the marked self-conceit which deludes them into the belief that they can resist when they wish and that further indulgence will make no difference. Among the very poor the grinding weariness of overwork and insufficient food drives them to seek temporary relief in alcohol, and before long what was first only a luxury becomes a dominating necessity. The false idea that alcohol is a tonic and strength-producer causes many of the poor to give alcohol to their children and thus lay the foundation for early

excess. In Bellevue Hospital, New York, in 259 young male alcoholics in whom there was no mental degeneration from chronic alcoholism and whose statements therefore may be deemed fairly accurate, 4 began before six years of age, 13 between six and twelve, 60 between twelve and sixteen, 102 between sixteen and twenty-one, 71 between twenty-one and thirty, and 8 after thirty years of age. Almost all gave a history of intemperance in other members of their families. The force of example is therefore often a potent cause of alcoholism; the fear of ridicule from their comrades and what is thought to be social necessity or a vain desire to be thought manly, are also factors in certain individuals. In the struggle to improve their position, individuals are often placed in new environments for which they are unprepared, or over-education for the position in life which by force of circumstances they must occupy, produces a mental dissatisfaction, with a consequent strain on their nervous systems, and, turning to alcohol for relief, they soon become addicted to its excessive use. Lives of idleness and pleasure-seeking, among the wealthy, not infrequently lead to alcoholism. In this country there is a little appreciated but not uncommon cause of alcoholism in the use of patent medicines and nostrums as tonics and cure-alls. A large number of these nostrums contain from 6 to 47½ per cent. of alcohol and they seem to be popular in ratio to their alcoholic content. Chronic alcoholism has thus been unwittingly acquired. Many acquire alcoholic habits in their endeavors to alleviate the pains of disease or disordered functions. The worries of life, business or domestic, and the desire for relief from sorrow, frequently cause men and women to seek oblivion in alcoholic narcosis.

While the environment of certain occupations is a factor in producing alcoholism, it is equally true that in other situations it produces temperance and sobriety. The demands of modern machinery and electrical devices require a clear mind and steady hands, both for the production of good work and also as a matter of self-protection, so that employers are more and more demanding sobriety among their employees. In the large centres of population these have been potent factors in the diminution of alcoholism among the younger working men. Judging from some 10,636 male alcoholics admitted to Bellevue Hospital, New York, the professions in which mental strain with worry, excitement and especially irregular hours, are a predominating factor, show a larger proportion of alcoholics than those in which such conditions are less pronounced. Journalists, actors, and physicians are thus more prone to alcoholism than lawyers, engineers and other professional men. Bookkeepers, clerks, accountants, and stenographers, seem as a class to show a high proportion of those who drink to excess. A craving for excitement as a reaction to what seems a monotonous existence, may account for the large numbers in this class of occupation. Those demanding physical exertion near fires, such as stokers, firemen, black-smiths, iron and brass moulders, have long been recognized as producing a craving for alcohol to relieve the physical exhaustion. Stable men, hostlers, hackmen, and teamsters of all kinds, men whose occupations vary with periods of hard work and rest and idleness, together with exposure to varying weather, form a large class in cities, who unfortunately acquire their habits of intemperance in the early and most pro-

ductive years of life. The age of more than half of the admissions in the large numbers belonging to these occupations was from five to fifteen years less than the age at which the greatest number of alcoholics was admitted to the hospital. Among the large number of men employed in the building trades in New York, alcoholism predominated in the following order: stone-cutters, plasterers, painters, masons, roofers and copper-smiths, plumbers and carpenters. From the opportunities and temptations of their occupation, saloon-keepers, bartenders and waiters show a high ratio of alcoholism. Among some 2,700 female alcoholics admitted to Bellevue Hospital, house work and domestic service was given as the occupation in more than half, but this, in a large but unknown number, really hid prostitution. Laundresses and cooks predominated among those whose definite domestic service was given. Seamstresses, dress-makers, and milliners comprised about six per cent. of the admissions and were more numerous than women working in factories and shops.

The influence of heredity is believed by some authors to be more potent than environment. Plutarch's saying that "drunkards beget drunkards" has been long recognized. Many descendants of alcoholic parents inherit a weakened and unstable nervous system. How large this proportion is to the total of such descendants it is impossible to calculate, but that it is large is undoubtedly true. The statistics of many institutions show that from 20 to 75 per cent. of these alcoholics have had either an alcoholic father or mother, or both parents given to such excesses. The compelling craving for alcohol in the parent is not inherited but a weak and unstable nervous system which renders the individual liable to excess in all things, and slighter indulgences lead quicker to the formation of the alcoholic habit.

It is of interest to note the relation of age to the admissions for various forms of alcoholism in Bellevue Hospital. For comparison, the ages of 10,636 male and 8,132 female admissions were taken. The largest number of admissions for males occurred in the period 33-37, and the largest number of females in the period 28-32. Up to the age of thirty-two there was a greater percentage of women than men. Between thirty-three and fifty-seven there was a greater percentage of men; at 58-62 and older, there was a slightly larger percentage of women. Of the women 20.8 per cent. were in the period of 28-32 and 19.9 per cent. of the men in the period 33-37. Of the women 17.2 per cent., and of the men 9.7 per cent., were younger than twenty-eight years; 37.9 per cent. of the women and 27.5 per cent. of the men were younger than thirty-three years; and 54.5 per cent. of the women and 47.5 per cent. of the men were younger than thirty-eight years. Through the three periods of twenty-eight to forty-two years there were 53 per cent. of the women and 57 per cent. of the men; through the five periods of thirty-three to fifty-seven years there were 66 per cent. of the men and 53.8 per cent. of the women. In the old age periods, after fifty-seven years of age, there were 7.6 per cent. of the women and 6.4 per cent. of the men. The greater relative number of young women is due to the facts that alcohol usually poisons women quicker than men and, among the working classes, the men, by a larger amount of muscular work, burn up more alcohol and thus escape some of its toxic action. These statistics are also influenced by the number of young prostitutes who

are necessarily included in the statistics from any large city. Alcoholism, as is well known, is more prevalent among men than women; during the ten years, 1895 to 1905, there were two and a half times more men than women admitted to Bellevue Hospital suffering from alcoholism.

The effect of season and other external influences is well shown by the admissions for alcoholism for the ten years, 1895-1905, in Bellevue Hospital. The total admissions in the alcoholic wards in that time were 43,916 males and 16,076 females. Considering the male and female curves for each of the ten years, there are some variations which are not shown in the average curve for the ten years. Periods of great heat cause a marked rise in the male curves but only a slight corresponding rise in the female curves. In some 630 cases of insolation collected in August, 1896, in New York, there was a history of alcoholism in nearly 90 per cent. and the men greatly predominated, there being 589 men, 40 women and 1 child.

Sociological conditions, such as labor strikes, cause a great increase of alcoholism among both men and women, as occurred in New York, in 1903. The variations in the Bellevue records show more varied and wider excursions in the male than in the female curves, and the rises and falls of the two curves in the same years do not always run parallel. Taking the average curves for the ten years by monthly admissions, the point of the January curves in both sexes is lower than the previous December; in February there is a distinct fall, reaching the lowest period of the year. There is a spring rise in March and April, a May fall, a June rise, a fall in July and August, a marked September rise and here the two curves separate, there being an October fall in the male and an October rise in the female curve, the point of the October rise being the highest point for the year in the female curve, a November rise in the male, the highest point for the year, and a November fall in the female and a December fall in the male and December rise in the female curve. Both agree in having the greatest number and highest daily average during the last four months of the year. Comparing the curve of the alcoholic with those of the general medical and surgical admissions, a striking difference is evident. The two curves are practically reversed for both men and women, as the greatest number of admissions for general diseases occurs in the first four months of the year. The curves for alcoholism here described are not those of the delirious cases alone, but are for all forms of alcoholism, the acute cases forming a minority.

Pathology.—There is no drug used in medicine about which more erroneous ideas have been transmitted than concerning alcohol, and the knowledge of the results of experiments on which is based our realization of its true action in the body, is not widespread among the medical profession. Ethyl alcohol is the one chiefly to be considered, but in the distillation of whiskies there occur other bodies as aldehydes, and some of the higher alcohols which are usually grouped together under the name of "fusel oil," and their action deserves consideration. In the compounding of cheap whiskies, and in their adulteration and manufacture, methyl alcohol must be considered by itself. In the ageing of wines, the ethers giving the various bouquets are not without their separate action.

Methyl Alcohol.—This is also called wood alcohol and is sold in the United States as columbian, colonial, union, or eagle spirits. In Canada, it is sold as greenwood or standard wood spirits. This is used instead of ethyl alcohol to adulterate the various essences or colognes and often to adulterate cheap whiskies. In experiments on the toxicity of the different alcohols, considering that of ethyl alcohol as 1, methyl alcohol is from .46 to .8, but this gives a false idea of its true toxicity when taken by man, although idiosyncrasies of resistance to methyl alcohol vary greatly, as the ingestion of two teaspoonsful of it has been followed by blindness; in other individuals many ounces have been taken, followed only by intoxication. Another peculiarity of methyl alcohol is that, except in very large doses, the serious toxic symptoms may be delayed for twenty-four hours or even several days. Even in animal experimentation, while more methyl than ethyl alcohol may be required per gram of body weight to cause death in one or two days, several observers have noted that methyl alcohol, administered to animals over long periods, causes serious nervous symptoms and produces pathological lesions in doses in which ethyl alcohol has little effect. The intolerance for methyl alcohol for long periods is due to the fact that a considerable portion of it is turned into formic acid in its passage through the body. The single constant pathological change found in animals after poisoning by methyl alcohol is fatty degeneration of the liver, the amount of fat extracted from the dried liver of dogs, thus poisoned, being over double the normal amount.

Recently Wood and Buller published 275 cases of methyl alcohol poisoning, among which there were 122 deaths and 153 instances of blindness. In New York City, in the winter of 1904–1905, there were 25 deaths from methyl alcohol poisoning, after drinking whisky adulterated with it. These authors emphasize the great idiosyncrasies to the toxic effect of methyl alcohol and give three degrees of intoxication. The first shows the ordinary marked symptoms of intoxication with dizziness, nausea and marked gastro-intestinal disturbances, terminating in perfect recovery in a few days, sometimes followed by more or less serious damage to vision. In the second degree, the dizziness, nausea, vomiting and gastro-intestinal disturbances are much more pronounced; there is marked cardiac depression, weak pulse, sweating and slow respiration; there may be delirium or unconsciousness which often deepens into coma and death. If coma once supervenes, recovery seldom takes place, for even if the patients recover consciousness, they usually relapse into coma and die. There is very often a sudden development of widely dilated, reactionless pupils, with complete or nearly complete blindness. After recovery, dimness of vision, often increasing to total blindness, is characteristic of this degree of poisoning. The third degree is that in which an overwhelming prostration comes on, which terminates in coma and death. Nearly all the severe cases which are not fatal, show characteristic bilateral, total blindness, coming on in a few hours or perhaps not for several days; this is followed by partial restoration of vision, which again, after days or weeks, gives place to a more or less complete and permanent blindness and atrophy of the optic nerve. In the majority of fatal cases, death seems to occur in less than twenty-four hours, though methyl alcohol may kill within an

hour or death may be delayed for one or two days or even longer. Considering the visual disturbances, in 41 instances there were 16 cases of total blindness, 3 total in one eye, 15 partial recoveries and 7 recoveries. In 35 patients, the sight became dim in 6, in from three to twelve hours; in 20, in twenty-four hours; in 5, in forty-eight hours; in 2, in seventy-two hours; in 1, in six days. The sight was lost in 2, in twelve hours; in 10, in twenty-four hours; in 5, in from thirty to forty-eight hours; in 12, from the third to the eighth day; in 1, in seventeen days. The ophthalmoscopic examination shows the visual field contracted, absolute central scotomata, the nerve head first congested, followed by gray or white atrophy and contracted vessels. Pathological examination shows a retrobulbar neuritis, papillitis, other inflammatory symptoms and atrophy of the optic nerve.

In those dead from methyl alcohol poisoning, at autopsy, intense congestion of the stomach and intestines, with a characteristic odor of methylated spirits, is noticeable. For the sake of conciseness, we will consider here the treatment of methyl alcohol poisoning. The treatment of the optic nerve atrophy is not very satisfactory in severe cases, although pilocarpine, sweat baths and potassium iodide as soon as the patient's condition permits, in the early stages of neuritis, followed by strychnine, hypodermically, seem to limit the extension of the secondary atrophy. The general treatment consists in washing out the stomach, and vigorous stimulation by strychnine, caffeine and digitalis, hypodermically. It seems useless to give these drugs by the mouth. Ergot, hypodermically, will also be found useful. High enemata, of warm saline solution or of glycerine and castor oil, should be given.

Higher Alcohols.—These, such as propyl, butyl, and amyl alcohol, are undoubtedly more toxic than ethyl alcohol and their toxicity increases as they mount in the chemical scale. This group, with substances such as furfural, compose what is generally called fusel oil. It has often been claimed that these alcohols cause many of the symptoms of chronic alcoholism, but recent work shows that they practically play no role in the acute or chronic poisoning. It is however claimed that the so-called moonshine whisky, produced in the mountains of some of the Southern states, is very deleterious if drunk when freshly distilled. The fresh rye or corn whisky would contain the greatest amount of fusel oil, for these higher alcohols are oxidized and changed into other substances, which give to old whiskies the various flavors, and the older they are, the less they contain of these substances. Huss has shown that amyl alcohol, in human beings, taken in doses of $\frac{1}{2}$ to $\frac{1}{4}$ grain, caused no toxic symptoms; doses of 1 to 2 grains were followed by sensations of oppression in the chest, with temporary feelings of dizziness; doses of from 3 to 4 grains acted as a gastrointestinal irritant, causing a burning sensation in the epigastrium, colic, vomiting and diarrhoea. He estimates that the total amount of amyl alcohol contained in twelve to fifteen glasses of brandy is only 1 to $1\frac{1}{2}$ grains, and the effect produced by this in ordinary drunkenness would practically be *nil*. Baer studied the effect of adding a definite percentage of these higher alcohols to ethyl alcohol, and found that the addition of 2 per cent. of amyl alcohol caused an appreciable increase in toxicity, and the addition of 4 per cent., a very considerable increase, so that a

severe type of poisoning resulted in animals. It is evident therefore, that larger percentages of these higher alcohols than are found in even the worst alcoholic beverages must be added to ethyl alcohol, before we can attribute to them any great share in the fatal outcome of an acute poisoning. Chittenden has shown that these higher alcohols, when present in amounts in which they are likely to occur in the alcoholic beverages, tend rather to increase, than to decrease, the rate of digestive action. Furfural, or pyromucic aldehyde, is also present in fusel oil. Joffroy has found that the toxic equivalent of this substance is 0.14 for rabbits and 0.20 for dogs as against 8.20 to 8.60, the true toxic equivalent of ethyl alcohol for these animals. But as a liter of rum contains only 0.015 to 0.040 grams, a liter of cognac 0.005 to 0.015 grams, if we assume that man is as sensitive as rabbits to furfural, it would require from 300 to 700 liters of rum or brandy to furnish the fatal dose. We must therefore leave out the consideration of this aldehyde in the conditions produced by ordinary alcoholic beverages.

Ethyl Alcohol.—This is the main constituent of most alcoholic beverages and to its action alone are due the symptoms of alcoholism as seen in man. The spirituous liquors contain from 47 to 56 per cent. alcohol; fortified wines, such as sherry, madeira and port contain about 18 to 22 per cent. The Sicilian wines, such as malaga and marsella, contain from 16 to 20 per cent., champagne about 9.2 per cent., the Rhine wines about 10 to 12 per cent. and the clarets 9 per cent.; of malt liquors, ale 5 to 8 per cent. and beer $2\frac{1}{2}$ to 5 per cent. of alcohol. Spirituous liquors may be considered as acting in ratio to their alcoholic content; the wines, however, vary in their action, either from the ethers which they contain or, in some instances, as far as digestion is concerned, in proportion to the contained solid matters, rather than to their alcoholic content.

After the ingestion of ethyl alcohol, the first action produced, aside from that on the mucous membrane of the mouth and stomach, is the flushing of the face and skin. This often follows small doses, which show no other effect upon the circulation. Sometimes a slight sweating of the hands and face accompanies this flushing. This may be due to a beginning paralysis of the vasoconstrictors, or as Meltzer believes, to a stimulation of the vasodilators or of some inhibitory function acting on the vasomotor centre and inhibiting its tonus. In either of these last two cases, it would be a stimulation, and not a paralysis, of a normal function. Most observers find that moderate doses dilate the peripheral capillaries without altering the blood pressure, and without any stimulation or depression of the heart action. The pulse rate is not altered after moderate doses, and an increase does not occur until doses sufficiently large to cause a fall in the blood pressure have been given. It has been long noticed, however, that a change in the character of the pulse does occur and it feels as if fuller and stronger after moderate doses of alcohol.

Some experiments of Kochmann give results opposed to some of the above conclusions, but furnish experimental proof for others. He found that in human beings, doses of 40 to 60 Cc. of a 10 per cent. or 40 to 50 Cc. of a 15 per cent. alcoholic solution, caused a rise in blood pressure. This reached its maximum 20 to 30 minutes after the ingestion of the

alcohol, and then gradually diminished until, after 60 to 75 minutes, it had entirely disappeared. This rise amounts usually to 15 mm. Hg. In some individuals, however, it was as much as 30 mm., but in others it amounted to only 5 mm. and in still other patients did not occur at all. Doses of 60 to 80 Cc. of a 20 per cent. solution or 50 to 60 Cc. of a 30 per cent. solution of alcohol caused at first a slight rise followed by a fall of blood pressure. A dose of 50 Cc. of a 50 per cent. solution of alcohol produced from the beginning a fall of arterial pressure, but this was not more than 10 mm. Hg. and 60 minutes after the pressure had risen to the ordinary height. These results could only be obtained in individuals who were complete abstainers or practically so. It was also noted that, after the rising blood pressure had reached its maximum, it was possible to keep it at this level by the administration of a second similar dose of alcohol. It was further found that the pressure could be kept up for four hours at the given height by administering alcohol at thirty-minute intervals and the blood pressure did not fall to its ordinary level until an hour after the last dose. During these experiments the frequency of the pulse remained practically constant, increasing only after large dosage with a fall of blood pressure. The size of the pulse was noticeably increased both to the palpating finger and in sphygmographic tracing; in the latter, the pulse excursion became greater and the dicrotic notch more noticeable. The rise of blood pressure seems due to stimulation of the vasomotor centre followed by contraction of the vessels of the splanchnic area, which overcompensates the peripheral dilatation. Large toxic doses of alcohol gradually lower the reflex excitability of the vasoconstrictor centres, dilating the arteries and capillaries of the splanchnic and peripheral areas, lowering the blood pressure, and acting directly on the heart muscle as a powerful depressant, weakening first the auricular and then the ventricular systole, causing more or less distension of both cavities and gradual diminution in the output of blood. The action of alcohol, therefore, on the circulation, after moderate doses, is a change in the distribution of the blood and perhaps an increase in the power of the heart's action without increasing the pulse frequency. In large doses, it paralyzes both the control of the vessels and the heart muscle.

Dilatation of the skin capillaries gives a sensation of warmth and there is increased radiation of heat from the body, but the temperature is seldom reduced more than 1° or 2° F. That very large doses of alcohol may cause a fall of 5° to 9° F. or even more, was exemplified in a patient whose temperature on admission was 90° and remained between 90° and 92° for fifteen hours; it then rose slowly to normal, reaching this point thirty-six hours after admission. The lowest temperature which has come under the writer's observation, was in a woman found comatose from alcohol, when the temperature of the air was about 6° above zero. After she had been in the hospital for three hours, wrapped in blankets, her rectal temperature was 80° F. The temperature reached normal twelve hours after admission. Such temperatures as these, in drunkards exposed to cold, are unusual, but by no means unique. Schäfer gives records of temperatures in drunkards after such exposure, of 79.5°, 86.6° and 83.1° F., the patients dying, while others, with temperatures of 72.2°, 76.4°, 82.2° and 86° F., recovered after a few days.

The respiration is directly stimulated by moderate doses—according to Binz—more in fasting and fatigued individuals, than after a meal or in non-fatigued persons. This direct stimulating action on respiration is not accepted by all, alcohol being often classed as an indirect respiratory stimulant. In large toxic doses there is a paralyzing effect on the respiratory centres, and the breathing becomes stertorous and slow.

In studying the effects of alcohol on the digestion, we find that it stimulates the flow of saliva and also the concentration and amylolytic power of human mixed saliva. This is purely a local reaction of short duration, ceasing when the alcohol is swallowed. Alcoholic fluids, when introduced directly into the stomach, do not stimulate the salivary flow. Upon gastric secretions, alcohol has a marked effect, increasing very greatly the flow of gastric juice and its content of acid and total solids, giving a juice of strong proteolytic action. Furthermore, this action is exerted, not only by the presence of alcohol in the stomach, but also indirectly through the influence of alcohol absorbed from the intestines. Any direct influence of alcohol on the pancreatic or intestinal secretions must be small, because of its rapid disappearance from the stomach by absorption. On the chemical processes of digestion, Chittenden has found that pure absolute alcohol has no very marked influence on the digestion of farinaceous foods by the saliva. The presence of 5 per cent. of absolute alcohol may lead to a slight increase in the digestive power of active saliva. Large quantities cause retardation of amylolytic action, but even 10 per cent. of absolute alcohol produces only slight retardation, hardly recognizable in the solvent action, but showing in the amount of reduced sugar formed. Whisky, brandy, wine, and malt liquors show a powerful inhibitory influence upon salivary digestion, out of proportion to their alcoholic content and due almost entirely to their acid properties. The influence of alcohol on the chemical action of gastric juice is *nil* when present from 1 to 2 per cent., and not until the digestive mixture contains from 5 to 10 per cent. of absolute alcohol is the action of the gastric juice materially interfered with. The malt liquors in small amounts are without inhibitory influence on the gastric juice, showing a tendency to slightly increase the rate of digestion. In larger amounts, they give rise to an inhibition of proteolysis, which is entirely unconnected with the small amounts of alcohol present, but directly traceable to the comparatively larger amount of extractives they contain.

There seems but little chance that alcohol, when consumed in moderate amounts, influences digestion in the small intestine, it being too rapidly absorbed to have much effect. Pancreatic juice, however, in its proteolytic action, is more sensitive to pure alcohol than gastric juice, 2 or 3 per cent. of absolute alcohol being sufficient to produce a distinct retardation of proteolysis. The acid substances contained in the spirituous liquors and wines have a more detrimental action on the proteid digestion of the pancreatic juice than the alcohol in these beverages. The extractives in the malt liquors likewise exert an inhibitory action upon the pancreatic proteolysis. The amylolytic ferment of the pancreatic juice, being similar to the salivary enzyme, is affected the same as in salivary digestion. Moderate doses of alcohol, taken not too frequently, would seem, as a sum total of their action, to favor an increase in the digestive processes,

but after repeated consumption, the digestive processes are perverted and diminished.

We know from the experiments of Atwater and Benedict, that after the absorption of alcohol, 98 per cent. of moderate doses is consumed in the body, the residue being excreted by the lungs and kidneys. It is used by the body for the needs of heat and muscular work, and in this way protects the body fats from consumption. It can, and sometimes does, protect the protein of food or body tissue from consumption, but at other times, in small doses, especially in persons not accustomed to its use, it fails to do this, even increasing the protein disintegration. In large quantities it is positively toxic; retarding or even preventing metabolism, and protein metabolism in particular. It is evident that alcohol, up to a certain amount, in healthy persons furnishes the equivalent of energy of the isodynamic amount of fats and carbohydrates, and the total amount of nitrogen under these circumstances must remain the same. The form in which nitrogen is excreted in the urine is often materially changed under the influence of moderate doses of alcohol. From the experiments of Beebe, in healthy young men on a given diet and in a state of nitrogenous equilibrium, when alcohol is given, the percentage of urea to the total nitrogen is diminished and the percentage of ammonia and uric acid are noticeably increased. The men used in these experiments were unaccustomed to alcohol and showed under its influence a slight increase in the total amount of nitrogen excreted. From the recent work of Folin, experiments on persons of low nitrogenous diet and on persons of high nitrogenous diet, show that the distribution of the nitrogen in the urine among urea and the other nitrogenous constituents, depends on the absolute amount of total nitrogen excreted *per diem*, but after taking this into account, the experiments of Beebe show that the uric acid and ammonia are increased and the urea diminished under the influence of only moderate doses of alcohol. From some yet unpublished work, kindly furnished to me by Fwing and Wolf of Cornell University, in the urine obtained from patients suffering from various degrees of alcoholism in Bellevue Hospital, New York, excreting from 10.3 to 17.4 grams of nitrogen in twenty-four hours, the urea nitrogen ranged from 64.7 to 84.1 per cent. of the total nitrogen. The percentage of the ammonia nitrogen to the total nitrogen ranged from 2.2 to 7.4 per cent. and the relative percentage of the amino acids to the total nitrogen from 4.8 to 14.4 per cent. Comparing this with the results given in Folin's work for normal individuals excreting over 10 grams of nitrogen, it is seen that in normal persons excreting from 14.8 to 18.2 grams, the percentage of urea was from 86.2 to 89.4 per cent. of the total nitrogen, the ammonia from 3.3 to 5 per cent. and the amino acids from 2.7 to 5.3 per cent. Comparing the above results, it seems fair to conclude that in some individuals suffering from chronic alcoholism, the percentage distribution of the substances forming the total nitrogen in the urine is materially altered in the ratio of urea, ammonia and amino acids to the total nitrogen. In three patients suffering from alcoholism, who excreted less than 10 grams of nitrogen in twenty-four hours, the ratios of urea, ammonia and amino acids to the total nitrogen did not vary to any greater extent than was seen in Folin's experiments with five healthy individuals excreting an equally low total nitrogen. In some of the patients in whom the

ratios mentioned deviated most from normal, postmortem examination showed the livers extensively diseased; whether this was a coincidence or not is uncertain. It is evident, however, that, although alcohol may be used by the body for energy, the metabolic changes are not similar, and it must be a question of some moment from whence the body draws its energy, whether it be alcohol, fats or carbohydrates. It is evidently possible for the body to use alcohol as a food material but the changes in metabolic results show that while being consumed as a food, alcohol may simultaneously exert its drug or toxic action.

As to whether alcohol is a source of heat when oxidized, Atwater found in his rest experiments, the heat given off from the body was equivalent to the total potential energy of the material oxidized. This was as true in the experiments in which alcohol made part of the diet as in those with ordinary food exclusively. Hence alcohol must have contributed its full quota of heat as did the starch or fat, and all its potential energy was converted into heat. The same principles apply in the work experiments and unless all the potential energy in the alcohol was converted into the energy of internal work in the rest experiments and into that of internal and external work in the work experiments, certainly an improbable hypothesis, part must have been transformed directly into heat in the body. The question whether the energy of alcohol is used for muscular work is not definitely settled. There is no evidence that there is a difference in the energy or heat derived from alcohol and from other nutrients, but there is no proof that such difference does not exist. It certainly seems, from these experiments, that probably such energy for muscular work is derived from the alcohol. It is Atwater's opinion that the utilizations of the energy of the whole ration are slightly less economical with alcohol than with ordinary diet, especially when the subjects were at hard, muscular work. For it was noticed that there were indications that the subjects worked to a slightly better advantage with ordinary rations than with alcohol. The possibility here shown of alcohol in moderate doses furnishing energy for muscular work is a far different question from the possibility of alcohol as a part of the diet for muscular labor. General observations, and the results of practical tests on a large scale, show such beverages to be of doubtful value or even harmful. Alcohol apparently increases the power of fatigued muscles, although it does not restore to them the same amount of power as they possessed before they were fatigued, and this restoration of power is only temporary and of short duration. It also lessens the sensation of fatigue, acting in some measure through the nervous system. To non-fatigued muscles it gives only a temporary increase in the work done. Alcohol will thus enable a brief spurt to be made, but it will not give sustained muscular power and is followed by a depression of energy to below the normal.

The action of alcohol on the brain is still a subject of dispute. Binz holds that alcohol first stimulates and then depresses; Schmiedeberg, Bunge, and others that the apparent stimulation of alcohol is a paralysis of the higher functions and that alcohol depresses from the beginning. Kraepelin claims to have proven from his experiments, that, in the early stages of its action, alcohol truly stimulates the motor functions of the brain, but that all reactions requiring nicety of judgment are dulled by even small doses. Kraepelin has also shown that small doses diminish the

accuracy and ability to add numbers or to learn numbers by heart. Smith has shown that this is especially noticeable when small doses of alcohol are taken daily, and that, when the alcohol is cut off, the ability to add and to memorize immediately returns. It is also noticeable that the tendency to erroneous judgments is increased, the subjects experimented upon believing that they had performed their reactions better under alcohol, when, as a matter of fact, the reactions were diminished in accuracy and rapidity. Alcohol in moderate doses does not increase the quantity or vigor of mental processes, and the flow of ideas with the feeling of mental richness is due to the removal of normal inhibitions. Alcohol clearly tends to lessen the power of clear and consecutive reasoning and decidedly lowers the acuteness of the senses. After large doses the judgment is lost, the powers of self-control and will are in abeyance, all idea of proportion is gone, the sense of responsibility and restraining impulse is destroyed, and finally, the motor power for speech and motion disappears and torpor and coma supervene. The result of the continued action of large doses is the permanent loss of these mental functions and the chronic alcoholic becomes an irresponsible animal.

Pathological Effects.—Since Anstie classified alcoholism as a nervous disease, it has been generally so considered. As concerns the relationship of man to his environment, the effect of alcohol on the brain is a predominant manifestation, but for the individual, the effect of alcohol on the heart and circulation in acute poisoning, and on the heart and abdominal viscera in chronic poisoning, is often more important. All the viscera are affected by chronic alcoholism, the cerebral symptoms dominating only because of the special function of the brain. Death from acute poisoning by alcohol is rare, and usually follows large doses in those unaccustomed to its use, or sometimes in children, who have accidentally swallowed a large amount of some concentrated alcoholic beverage. The lesions found at autopsy do not correspond to the severity of the symptoms. There is an intense overwhelming of the functions of the various organs, which occurs so quickly that it leaves no corresponding anatomical change. Thus a young, healthy man who had been drinking heavily all day, after sitting quietly, attempted to walk across the ward and dropped dead; the autopsy showed no cause for death. Death may occur suddenly, as in this case, after several hours of drinking, or within half an hour, or coma may suddenly come on after several hours and be fatal. In such acute poisoning, if death follows soon, the body may resist decomposition for an unusual length of time. The stomach and tissues may even have a more or less well marked alcoholic odor. The stomach, œsophagus, and duodenum may be of a deep red color, with, at times, punctiform ecchymosis in the gastric mucous membrane. There is at times, but not constantly, a venous congestion in some of the viscera and the bladder is often greatly distended. There is frequently congestion and sometimes extravasation of blood or œdema in the brain and its membranes. There may be a serous effusion in the ventricles. In one young woman, thirty-two years of age, previously a total abstainer, who took enormous amounts of alcohol, dying after four days' poisoning, the brain showed acute encephalitis with marked cellular degeneration; the spinal cord showed degeneration in the posterior tracts and in the cells of the anterior horns. The peripheral nerves were normal.

Microscopically, the nerve cells show two different lesions. One, as shown by the Goigi method, is the so-called moniliform change, characterized by the appearance of irregular swelling from varicosities in the course of the protoplasmic processes of some of the nerve cells, associated with partial loss of the delicate bud-like or spinous projections normally present in these processes. The second change is that of chromatolysis, and is shown by the disintegration of the small chromatin granules, known as the Nissl bodies, as brought out by the stain of that name. These changes are not in ratio to the severity of the symptoms and as Welch says, they do not represent any serious permanent damage to the nerve cells, but are rapidly recovered from after the disappearance of the causative factor. They seem to be the only significant anatomical change produced by acute alcoholic intoxication. These changes are not general and occur only in a minority of the cells, but they have been found in the cells of the cerebral hemispheres, the cerebellum, medulla, the spinal cord and the sympathetic ganglia.

In studying the lesions of chronic alcoholism, one is forcibly struck by the great variations in their intensity in the various organs of different individuals. Personal idiosyncrasy is as marked in the lesions produced by alcohol as it is in the susceptibility of different individuals to the same dose. In 1 person, the brain may show the greatest change, and in another, the heart and arteries seem chiefly affected; in others, in may be the liver, or the kidneys, which seem to have borne the brunt of the toxic action. In studying the age at which death occurs from various forms of chronic alcoholism, there is a noticeable difference between the sexes. Taking 541 deaths from alcoholism in Bellevue Hospital, New York, 318 men and 223 women, it is noticeable that the highest percentage of the men died in the same quinquennial period in which there were the greatest admissions, while the greatest percentage of female deaths was ten years later than the period of greatest admissions; thus 20 per cent. occur in men between thirty-three and thirty-seven years of age, and 19 per cent. of the deaths in woman occur between thirty-eight and forty-two years of age. This is undoubtedly due to the prevalence of pneumonia at these ages. Between thirty-three and forty-two years of age, both sexes show practically the same percentage (men, 34.4, women 38.2). But there is a very great difference in the number of deaths before thirty-two years of age, the percentage in men being 17.2 and in women 31.4; that is, nearly twice as many young women die of alcoholism as young men. The fact that a large number of young prostitutes are necessarily included, accounts for the larger number of young women dying from alcoholism. From the same causes, there are, both relatively and actually, more fat alcoholic women than men and the bodies of the great majority of both sexes are well nourished, and this is striking, when we consider for what long periods these patients subsist on alcohol alone, without other food; it also shows well the possible food action of alcohol. The fine, white, smooth skin of most chronic alcoholics is noticeable, due partly to accumulation of fat beneath the skin and partly to atrophy of the skin itself. To obtain an idea of the lesions in chronic alcoholism, the records of 125 cases are taken from the post-mortem reports of Bellevue Hospital, 90 of which were men and 35 women. These were not chosen because they showed certain lesions, but

because the patients had given a definite history of alcoholic excesses. Many histories with pneumonia have purposely been rejected.

In the heart, we find lesions resulting from direct poisoning and from associated conditions. Fatty degeneration of the muscle is the most common lesion, brown atrophy combined with fatty degeneration is the second most common, brown atrophy alone the third, and fibroid myocarditis the fourth. There are often various combinations of the above lesions, and while fatty infiltration is said by most observers to be more common than fatty degeneration, the reverse held true, in my experience. That brown atrophy of the cardiac muscle is caused by alcohol seems to be true, for after excluding all cases in which carcinoma was present and in which there were any signs of healed or active tuberculosis, in the 125 cases, there remained 23 hearts from individuals under fifty-five years of age in which this degeneration was present. The secondary effect on the heart is shown through the circulatory system, and from disease of the coronary arteries we obtain fibroid myocarditis; and the enormous hypertrophied hearts of beer-drinkers are produced by the large amount of fluid passing through the bloodvessels. The arteriosclerosis produced by alcohol or secondary to the kidney lesions produced by it, is also a cause of the cardiac hypertrophy and later of the fibroid myocarditis. Sudden death not infrequently occurs in young alcoholics, who, possessing a heart with fatty degeneration, further poison it with alcohol, and when some sudden muscular action causes a sudden strain on the cardiac muscle, it fails, and death results. Alcoholic poisoning is usually considered as a cause of arteriosclerosis and atheromatous degenerations. Lancereaux states that atheroma of the aorta and vessels is so rare in alcoholism that its presence almost excludes alcoholism. Certainly the experience in this country is widely different; it is characteristic of arteriosclerosis that lesions are unevenly distributed in the body, and the peripheral arteries may remain unaffected, while the aorta or central arteries may be extensively degenerated. Atheromatous degeneration is a frequent cause, in alcoholics, of aneurism, apoplexy, and embolism. Cabot, in studying the frequency with which arteriosclerosis may be made out in the radial arteries in alcoholics, comes to the conclusion that it is not noticeably present in more than 6 per cent., but the atheromatous degeneration from alcohol is more commonly present in the aorta and large vessels of the neck and in the cerebral and visceral arteries than in the peripheral. It is usually uniformly extensive in the aorta and vessels, although it is sometimes extensive in the aorta and but slight in the vessels of the neck, and in other cases, the reverse is true. The aorta and vessels may show very slight atheromatous changes and yet the coronary arteries be extensively calcified. In 53 men dying under fifty years of age, atheroma was extensive in 9, moderate in 26, slight in 14 and absent in 4. In 19 women atheroma was extensive in 6, moderate in 6, slight in 6 and absent in 1.

The most common conditions found in the lungs are œdema, congestion, and the various forms of pneumonia, such as lobar, broncho-septic; and aspiration pneumonia is not infrequent, especially in those who have serous meningitis and inhale particles of food. It is also very common to find tuberculosis in various stages; the old idea that alcohol is preventive of tuberculosis is proven to be unfounded and it is unquestionably true

that alcoholism reduces the resistance of the body and distinctly predisposes to tuberculous infection. Pulmonary emboli from cardiac thrombosis and embolism of the pulmonary arteries were also found in this series.

The liver has always been considered as especially prone to show changes from chronic alcoholic poisoning with fatty degeneration and cirrhosis as the two special forms of degeneration. Rosenfeld has found that a fatty liver can be produced in dogs, if they be starved for six days and then fed on alcohol, and by this method, after more than four doses of $3\frac{1}{2}$ to 4 Cc. of 96 per cent. alcohol, the fatty content of the liver increases over the normal 10 per cent. in starving dogs to an average of 22.6 per cent. If sugar be given with the alcohol, fatty degeneration does not take place. This seems to indicate that the frequency of fatty degeneration in man may depend in some measure on the common abstinence from food among alcoholics. It is very noticeable clinically, that those who partake of large amounts of malt liquors are especially prone to fatty degeneration of the liver. In the 90 livers of men examined, fatty degeneration occurred in 37 per cent., and, of the 35 women examined, it occurred in 40 per cent. In combination with cirrhosis, brown atrophy and parenchymatous degeneration, fatty degeneration was present in 43 per cent. of the men, and 34 per cent. of the women. That is, it was present in 80 per cent. of the livers examined of the men and 74 per cent. of the women. Fatty degeneration combined with cirrhosis was the second most common lesion, being seen in 31 per cent. of the men and 17 per cent. of the women. Animal experimentation has not yet proven that progressive cirrhosis of the liver is produced by alcohol, but clinically we find a well defined history of excessive alcoholic indulgence in the great majority of patients suffering from cirrhosis. The fact that it occurred in almost one-half of the men and over one-third of the women examined in the necropsies under consideration, would certainly indicate its alcoholic origin. The term cirrhosis, here used, is meant to designate an increase in the connective tissue, whether the liver was larger or smaller than normal or of normal size and weight.

The enlarged cirrhotic liver seems to be the most frequent, and the true biliary cirrhosis, the least frequent. Clinical experience in Bellevue Hospital, New York, suggests that the extreme degrees of cirrhosis do not occur so commonly as they did fifteen or twenty years ago. This is probably due to the greater use of malt liquors. Lancereaux believes that, in Paris, those who drink wine in excess are the most prone to suffer from cirrhosis of the liver. Whisky, gin, and rum are more likely to produce the atrophic form of cirrhosis and the contracted hob-nail liver. The exact process by which cirrhosis is produced is still a disputed point. Alcohol is a cellular poison, causing degeneration and death of cells, which may be followed by an increase in connective tissue and thus be the chief cause of cirrhosis, or since acute and chronic congestions are at times followed by an increased growth of the fibrous tissue, the cirrhosis may result from the chronic hyperæmia produced by the dilatation of the vessels and congestion resulting from the incessant doses of alcohol. Rosenfeld expresses the view with considerable reserve, that cirrhosis of the liver is the result of very long continued alcoholic poisoning with doses which cause most men to succumb; this he believes would explain the infrequency of cirrhosis

relative to the large numbers of alcoholics. In the reported cases of children suffering from cirrhosis of undoubted alcoholic origin, it is noticeable that the disease seems to follow more quickly and from smaller doses than in adults. In the Bellevue Hospital necropsies it was present in some degree in 48.8 per cent. of the men and 34 per cent. of the women. It is a very striking fact that in not a single individual of the 125 examined was the liver reported normal.

In the spleen, chronic congestion and fibrosis are the two most common pathological conditions. Chronic congestion was found in 30 per cent. of the men and 66 per cent. of the women, fibrosis in 25 per cent. of the men and 18 per cent. of the women. Acute congestion occurred next in frequency; other conditions found were brown atrophy, amyloid degeneration, hæmochromatosis and brown atrophy. Perisplenitis is recorded in 4 patients. In 4 men and 1 woman the spleen was normal.

In the pancreas, the great frequency with which chronic fibrosis occurs is very noticeable. In the seventy-four times in which the pancreas is mentioned in the men, chronic fibrosis occurred in 52 per cent. and in 29 women it occurred in 50 per cent. Fatty infiltration occurred in 16 per cent. of the men and in 14 per cent. of the women. The pancreas was mentioned as normal in 23 per cent. of the men and in 25 per cent. of the women. It was atrophic in 3 patients and hemorrhagic in 1 man and 1 woman. The adrenal bodies, in 70 men, showed fatty degeneration of the cortex in 34 per cent., and in 21 women this lesion was present in 57.5 per cent. These bodies were mentioned as normal in 58 per cent. of the men and in 38 per cent. of the women.

There has been much discussion as to the effect of alcohol upon the kidneys. It has been frequently demonstrated, as Welch points out, that the urine, even after a single alcoholic excess, often contains abnormal elements, indicative of transient irritation or of slight inflammation. In animal experiments, von Kahlden has shown that in dogs there occurs a fatty degeneration and necrosis of the renal epithelium, hyperæmia of the veins and capillaries with hemorrhages, and he considers that with longer duration of the experiments, chronic interstitial nephritis would appear as a result. Formad found in alcoholics, who died suddenly, a marked hyperæmia of the kidneys with noticeable enlargement in beer-drinkers. The enormous amount of fluid taken produces a functional hypertrophy. When arteriosclerosis has developed, the chronic forms of kidney disease necessarily follow. It has been very noticeable in the autopsy experience of the author that there are no records of normal kidneys; all examinations showed some lesions, chronic ones greatly predominating. Acute nephritis was mentioned in only 2 men and 1 woman. Acute inflammation grafted on chronic nephritis was present in 7 men and in 1 woman. Chronic parenchymatous nephritis, often with congestion, was the most common lesion, being present in 60 per cent. of the men and in 63 per cent. of the women. Chronic interstitial nephritis, at times with congestion, occurred in 39 per cent. of the men and 29 per cent. of the women. As these examinations were made on patients from twenty to over seventy years of age who had died from chronic alcoholism, it would seem to show that while the kidneys for years may escape, and personal idiosyncrasies vary greatly the intensity of the lesions in various organs, sooner or later the kidneys are certain to become diseased.

The stomach shows various forms of gastritis; chronic gastritis is one of the commonest lesions. An inflamed gastric mucosa, covered with ropy mucus, is common from acute alcoholism, and the acute sooner or later goes on into the chronic form. Chronic atrophic gastritis was present in 50 per cent. both of the men and the women examined. Hemorrhagic gastritis was present in 24 per cent. of the men and in 16 per cent. of the women. These two conditions were not infrequently combined. The mucosa of the intestines does not suffer so much as the gastric mucosa. The most common condition found is congestion, sometimes with œdema. In about 50 per cent. of the patients examined the intestinal mucosa was normal.

The bladder is very apt to be over-distended in patients who have died suddenly or had unconsciousness before death. It may even be ruptured as was the case in two men in the service of the author. In about 25 per cent. of both sexes we found the lesions of either acute or chronic cystitis.

That alcohol tends to produce sterility has long been known. In 5 among 12 women between twenty and thirty years of age, the ovaries were markedly atrophic, appearing like those a number of years after the menopause, and, in women between thirty-one and forty, they were atrophic in 5 among 8. Thus in half of 20 women under forty years of age, they showed extensive atrophy. In the men, the testicles did not show gross evidences of atrophy, but, in the few examined microscopically, there was sclerosis. Lancereaux has proved this and Simonds observed that in 60 per cent. of chronic alcoholics on postmortem examination, azoöspemia was found. Broun and Garnier have confirmed by animal experimentation this atrophy of the testicles following alcoholic ingestion.

It has long been recognized that alcohol has a special affinity for the higher nervous centres, and especially on those coming more into the clinical aspect of the disease. Inherited or acquired constitutional defects cause great variations in the effects of alcohol upon individual nervous systems and it is difficult to estimate the difference between the lesions caused by alcohol in previously normal persons and in those inheriting various defects. That a previously weakened nervous system will show earlier and more extensive lesions seems logical and is probably true, but the idiosyncrasies of normal persons to alcohol present wide variations. There seems no question that serious nervous diseases in persons of previously normal constitutions are produced by alcohol. Some individuals will die of various somatic degenerations and still retain apparently normal cerebral tissues, while, in others, the brain and spinal cord seem to suffer early, and disproportionately, compared with the heart and abdominal viscera. The lesions in the central nervous system seem to be brought about either from the degeneration of the cerebral arteries or from the direct action of alcohol on the nerve cells. In examinations of given brains, it is difficult, or often impossible, to differentiate how much the changes are due to one or other of these causes. Œdema and congestion of the membranes are usually present, especially the former, and this ordinarily extends into the cerebral tissue itself and was mentioned as present in 72 per cent. of the 76 brains of the men and in 51 per cent. of the 29 brains of the women examined by us. Congestion of the cerebral tissue

was found in 54 per cent. of the men and in 14 per cent. of the women. Adhesions of the dura to the skull, with increase in the Pacchionian bodies, are common, and very frequently there is thickening, opacity, and adhesions of the pia. Chronic meningitis was observed in 65 per cent. of the men and in 41 per cent. of the women and, combined with this, atrophy of the convolutions was found in 31 per cent. of the men and in 41 per cent. of the women. Cerebral degeneration seems to be more common among women and corresponds with the clinical experience that women degenerate mentally from alcoholic excesses more quickly and more completely than men. Pachymeningitis is not uncommon and pachymeningitis hemorrhagica is not infrequently seen in alcoholics, probably from trauma acting on the diseased vessels. All inflammations in alcoholics seem to be prone to the hemorrhagic type and hemorrhagic meningitis was present in three men. The degeneration of the vessels produced miliary aneurysms and it is not uncommon to find recent cerebral hemorrhages or encysted old hemorrhages or areas of cerebral softening from cerebral embolism.

Microscopical examination of the cerebral tissues shows an intense degree of atheromatous degeneration of the minute vessels which are enlarged, often tortuous, unevenly distended, usually by fusiform dilations, and their tissues covered with nuclear proliferations. About these vessels the spider or glia cells are crowded in great abundance. These so-called scavenger cells form, with their branching processes, a thick connective tissue felting, densest just underneath the pia, converting the outer fourth of the cortex into a closely matted layer, much diminished from the normal thickness and often clearly mapped off from the layers beneath. Sometimes the cellular elements of the glia predominate, but in later cases many of the protoplasmic masses have disappeared, leaving a dense connective-tissue structure in which the remaining nuclei are thickly sprinkled. The perivascular spaces are often filled with lymphoid cells. The second and third layers of the cortex show but little change, but according to Bevan Lewis, a few of the low, pyramidal cells may be degenerated; the fifth layer of motor cells shows extensive fatty degeneration and, with the spider cells beneath, is undergoing disintegration and absorption. The cells show a marked degeneration of their apical processes and, in many, these have disappeared. The axis cylinder shows a loss of medullary investment and is itself greatly swollen and often irregularly fusiform. The bodies of the motor cells are swollen, rounded, and constantly show an abnormal, coarsely defined boundary wall with pigment crowding against the cell body, which also shows vacuolization and often extensive chromatolysis. The white matter of the cortex shows equally extensive atheromatous changes in its vessels and in the fusiform and sacculated dilations are seen deposits of hæmatoidin granules. Not infrequently the vessels are plugged and the diseased wall found ruptured with extravasated blood and hæmatoidin crystals in the surrounding areas. The changes found in the spinal cord are similar to those of the cerebral cortex. The vessels of the posterior and lateral columns are more involved than those of the anterior columns. The characteristic change is an obliterating endarteritis, the lumen of the vessel being encroached upon to such a degree that the intima is folded into ridges. At times the vessels are even occluded by this process. The pia of the cord

often shows thickening and evidences of inflammation, an extension downward of chronic meningitis of the cerebral pia or a coincident chronic inflammation. The connective-tissue processes from the pia into the cord are thickened, the median raphé of the posterior columns and the peripheral zone of the cord being the areas of election for the sclerotic processes. The anterior and posterior nerve roots are sometimes involved. The degenerative processes may be unilateral or bilateral and the various segments of the cord show varying and irregular degrees of involvement.

The paralysis produced by the peripheral neuritis was described by older writers, such as Magnus Huss, as due to lesions in the central nervous system. When the peripheral lesions were fully studied the local changes were deemed sufficient to account for all symptoms and the central nervous system was not considered as involved. The changes in the nerves were described as of two types: the first in which the degeneration of the axis cylinder was primary, the second the interstitial type, in which hyperplasia of the endoneurium and perineurium were primary, pressure atrophy following in the axis cylinder process. The acceptance of the neuron theory has caused us to revert to the ideas of the older writers and realize that, in the vast majority, the neuritis of alcoholics is of central origin. In a series of cases of alcoholic neuritis occurring in Bellevue Hospital, Dr. Harlow Brooks, with whom the work of the author in the pathology of alcoholism has been done, has studied the central nervous systems and peripheral nerves. In one patient the peripheral nerves alone showed the degenerative changes; the most diligent search with the Marchi method failed to show any corresponding changes in the cord. It is possible therefore that alcoholic neuritis may be due to involvement of the peripheral nerves alone, but we are led to believe that such are very exceptional. In some of the other cases there was marked degeneration in the cortical cells of the cerebrum, especially in the motor areas, accompanied by degeneration of descending fibers in the internal capsule and in the descending columns of the spinal cord; not a true tract degeneration but one of isolated and often widely separated fibers. In the spinal cord, extensive cytoplasmic degeneration was present in the ganglion cells of the anterior horn, the ventrolateral group being especially studied, and there were invariably isolated degenerated fibers in the anterior nerve roots. Degenerated fibers were found in the ascending tracts of the spinal cord, particularly in the severe cases, this being accounted for by alterations, at times very marked, in the ganglion cells of the posterior roots. In some cases ascending and descending degenerations were present in the same spinal cord. Similar results have been found by numerous other investigators.

The special staining of nervous tissues by the Nissl and Marchi methods at first raised hopes that, in delirium tremens, some lesions would be found in the brain and spinal cord which would correspond to the clinical symptoms. But so far these hopes have not been entirely fulfilled. Although the Nissl cell changes were found in all cases of delirium and in chronic alcoholism, Marchi's degeneration change was not found in pathological amounts in all cases of delirium nor in the chronic alcoholism without delirium. The changes in the bloodvessels and connective tissue in delirium tremens seem to run parallel to the intensity of the chronic alcoholic processes. Apart from the tendency of the chronic arterio-

sclerosis to cause hemorrhages, there is in delirium tremens a distinct tendency to minute, acute hemorrhages which are diffusely scattered and numerous in the cerebral cortex in the central and frontal convolutions, less frequent in the cerebellum and still less common in the spinal cord. They lie in the tissues, at times unaccompanied by a bloodvessel, and often there is a thin layer of red cells along a vessel. The place of predilection for these hemorrhages is the region of gray matter around the third ventricle and the aqueduct of Sylvius. They vary in size from minute areas to the size of a bean; a concomitant acute inflammatory process does not occur. These hemorrhages are very commonly observed in the regions of the nuclei of the oculomotorius and abducens nerves. Taking all the pathological changes into consideration, it cannot be said that delirium tremens presents a specific pathology.

The pathology of Korsakow's psychosis is a combination of what has already been described. This has the dura adherent to the skull, the thickened pia with its gray striations along the course of its vessels, the diffuse cerebral atrophy and increase of the connective tissue, the cellular degenerations shown by Nissl's staining and other changes produced by chronic alcoholism. There is the same tendency as in delirium tremens to small hemorrhages in the cortex, spinal cord, peripheral nerves and especially in the regions of the nuclei of the third and fourth nerves. These may extend down into the fourth ventricle and involve the nuclei of the vagi. They occur only in patients succumbing in the early stages but in those who die later there is still evidence of previous hemorrhages. The spinal cord shows degenerations in the various tracts, and of the spinal neurons. The peripheral nerves show the various lesions of neuritis or stages of reconstruction.

That alcoholism reduces the resistance to infectious diseases has long been known and is generally recognized. This increased liability to disease is undoubtedly true in the temperate and northern climates. In the tropics, however, while the statistics from the British army seem to prove the same for India, a recent article by Major Woodruff gives statistics for the American troops in the Philippines which go to show that the moderate and even excessive drinkers, after two years residence, were in far better health, and much more able to throw off disease than the total abstainers. In the temperate zones an attack of an infectious disease in a chronic alcoholic is exceedingly prone to cause delirium tremens and the prognosis under these circumstances is always grave. Barthelemy emphasizes the fact that waiters and workers around saloons acquire an especially severe form of syphilis. Bärtsch shows that in epidemics of cholera, the disease claims the majority of its victims among the alcoholics and, when they are attacked, the chances for recovery are relatively small. In pneumonia, the mortality among the alcoholics greatly exceeds the average. In Bellevue Hospital, New York, in 1904, there were 1,001 patients with lobar pneumonia; of these 667 gave a history of alcoholism. Among these the mortality was 50 per cent. and among the non-alcoholics 23.9 per cent.

The moderate use of alcohol is a relative term; moderation for one is excess for another. Duclaux defines excess as any amount of alcohol, any effects from which, one remains conscious of, an hour after its ingestion. Many moderate drinkers use alcohol throughout a long life and show no ill

effects from its use, while others find after a longer or shorter period that it has insidiously produced nephritis, gout, degeneration of the liver, or arteriosclerosis and that their viscera are permanently damaged.

The results of chronic alcoholism unfortunately do not end with the individual; the children of alcoholics often come into the world as idiots or weak minded. Howe, in Massachusetts, found that 145 of 300 idiots were descendants of drunkards, and that among the poorest classes of the population, not one-quarter of the parents who had idiotic children could be considered as abstinent. Beech, in England, found in 430 idiots that 31.6 per cent. were children of alcoholics. Bourneville, in Paris, found that of 1,000 idiotic epileptics and weak minded children, 471 had a father who was alcoholic, 84 an alcoholic mother, and in 65 both parents were drunkards. Only in 209 of these cases were the parents not alcoholic. In Normandy, Dahl found from 50 to 60 per cent. of the idiot children had either an alcoholic father or mother. In Sweden, Lovens ascribes drunkenness in the parents as the cause of 25 per cent. of the idiots. It was noted that, in Norway, from 1825-1835, following the free distillation of brandy, drunkenness enormously increased and simultaneously the number of idiots increased 150 per cent.; afterward, in the ten years from 1855-1865, when the consumption of brandy had greatly diminished, the number of idiots diminished 16 per cent. simultaneously with an increase in the population of 14 per cent. Bezzola, in Switzerland, studied 70 cases of pronounced idiocy and found that half of these idiots were generated during the wine harvest, New Year's week and the Carnival; that is, in the fourteen weeks in which the Swiss chiefly carouse, while the rest were divided evenly over the remaining thirty-eight weeks in the year. The normal generation curve of Switzerland showed on the other hand that during these same periods of feasting there was a noticeable diminution in the number of children generated.

Epilepsy in children frequently follows alcoholism in the parents. Spratling mentions that while alcoholism is not usually a direct cause of epilepsy in women, it is frequently an indirect cause through its presence in the parents, nearly always in the father. Féré found, in France, that among 308 male epileptics, 118 were descendants of alcoholics and of 286 females, 130 were descendants of alcoholics. Kawalewsky, in Krakow, could prove drunkenness in 60 per cent. of the epileptics. Wartman found, in Germany, the same history in 130 of 452 epileptics. Blueler, in Switzerland, could prove drunkenness in the progenitors of 70 per cent. of his epileptics. Congenital deafness and dumbness do not seem to be produced by alcoholism in the parents in any large number of the children showing these afflictions. Chronic hydrocephalus seems to be more frequently the consequence of alcoholism in the parents, for, in Berne, 23 of 38 children suffering from this disease had alcoholic parents; in Paris, 18 out of 23 had drunken parents.

That alcoholism tends to the degeneration of the race, and after a few generations to extinction, has been abundantly shown. Legrain observed 215 alcoholic families, in three generations of which 814 members were hereditarily tainted; 197 of these were alcoholic, 322 were weak minded or idiots, 161 stillborn, 37 prematurely born, 121 died shortly after birth, so that 496 were either mentally or physically degen-

erated. That 174, or 21 per cent., were stillborn or died so shortly after birth that they showed inability to continue their existence, is a striking example of the effect of alcohol on the unborn child. Demme observed ten alcoholic families and compared them with ten non-alcoholic families; in the alcoholic families, among 57 children, 25 were stillborn or died in the first month of life, 22 were designated as sick, and 10 as healthy, while in the non-alcoholic families, 5 were stillborn or died early, 6 were sick, and 50 were healthy. Only 17.5 per cent. in the alcoholic families were healthy, while practically only 18 per cent. in the non-alcoholic families were not healthy. Of the 37 children in the seven families in which either the grandparents or the mothers were alcoholic, only 2 children were normal. Sullivan found that from 120 female alcoholics there were 600 children, and of these 335 died under two years of age or were stillborn; in more than 60 per cent. of these cases the children died from convulsions. He found that 21 of these alcoholic women had sisters or daughters who were abstinent and who had children from temperate men; these 21 alcoholics had 125 children, of whom 55.2 per cent. died before the second year of life and the 28 non-alcoholic women had 138 children of whom 23.9 per cent. died before the second year of life. The mortality of children from alcoholic mothers is thus 2.5 times greater than from non-alcoholic mothers in these statistics. Animal experiments shows the same relative mortality between alcoholic and non-alcoholic animals.

Morel draws attention to the fact that individuals who are given to alcoholism in their youth as well as the descendants of drunkards, are noticeable for their small stature and feeble, muscular development, presenting a type of infantilism. Lancereaux compares this condition with the descendants of the tuberculous and considers that infantilism is especially marked in the descendants of the tuberculous alcoholic; thus he believes that, pushed to its extreme limits, alcoholism creates a special race as it were, which can continue itself for a certain period with its physical infirmities and vicious tendencies, but happily it lacks the elements sufficient to reproduce itself for any length of time; with its descendants cursed with impotence and sterility, it is not slow to disappear.

DELIRIUM TREMENS.

Etiology.—Delirium tremens develops on the foundation of chronic alcoholism. Its occurrence does not run parallel to the amount of alcohol taken, for idiosyncrasy is usually as strongly marked here as in all conditions in which alcohol comes in question. Many men who have never been intoxicated, but who have for years steadily taken alcohol will, after some severe accident, develop delirium tremens. Its occurrence as far as climate, age and sex are concerned, is the same as for chronic alcoholism, but it differs essentially in its seasons of greatest frequency and is dependent for its development on other causes, which are engrafted on the chronic alcoholism. It occurs more frequently in northern regions and in the great industrial centres. Where beer and wine are the predominating drinks, delirium tremens is less frequent than in the countries in which men drink spirits chiefly. It has been

claimed that since the distilled liquors contain less fusel oil there are fewer numbers of delirious cases, but it is doubtful whether any such deduction is justifiable. The writer has often noticed that delirium tremens patients who had consumed only high grade whisky, seem to clear up quicker than those who had consumed a cheaper grade, but even in these cases the doubt always remains whether or not less ethyl alcohol has been consumed. When one realizes that a pint of cheap whisky may be purchased for ten cents, and that not infrequently, at least among the Bellevue Hospital patients, a pint is reckoned as a single drink, even careful calculations on the amount consumed may go astray.

The time of year shows a distinct influence on the number of delirious cases. Bonhoeffer, in Breslau, says that the winter months, January, February, and March, show the lowest numbers; from April on there is an increased frequency which reaches its highest point in July and August. The curve maintains almost the same rise through September, and falls rapidly in November and December. He quotes Näcke as having noticed essentially the same differences in Königsberg. The occurrence of delirium tremens in Bellevue Hospital corresponds with the above statements in so far that sudden heat always shows an increase as seen in July, but there are more patients suffering from delirium tremens during the winter months than in the spring and fall, and the number during the cold months is equal to or even greater than during the hot months. This is due undoubtedly to the large number of pneumonia patients and to the greater number of accidents, such as fractures, in the cold months, but even after deducting these, the total remaining is as high among some of the cold months as during any of the hot months. These statements are based on the statistics of 1,066 cases of delirium tremens occurring between January, 1904, and July, 1905. It would seem therefore that the varying occurrence of delirium during various seasons of the year is largely affected by other well known accidental causes which do not seem to act in different places with even intensity. The previous duration of chronic alcoholism seems to have more influence, and it is said that the average is from six to ten years, although according to Jacobsohn it is never less than seven years. The age at which delirium tremens develops is the same as that in which chronic alcoholism is most common, that is, between thirty and fifty years. In children it is rare. Bonhoeffer quotes one of sixteen years of age, and the writer saw one boy of fifteen years. It occurs most frequently in men, doubtless because they are more exposed to various accidents, which tend to bring about an outbreak. By some it is claimed that the delirium in women is shorter and less severe than in men; this does not correspond with the opinions of others, although in my experience the delirium in women is usually of a less violent type. It is impossible to say to what extent inherited or acquired mental degeneration influences the occurrence of delirium tremens in chronic alcoholics but that such defect of mental vigor is present in the majority, is beyond question. It seems certain, however, that succeeding attacks of delirium tremens are more easily brought about than the primary one.

Accidental causative factors producing delirium tremens in chronic alcoholics have long been recognized, such as acute infections, trauma,

hemorrhage, epileptic attacks, the sudden withdrawal of alcohol, sudden intensity of alcoholic excesses or mental shock. Bonhoeffer, in 250 cases of delirium tremens, could prove in 70 per cent. a recent acute illness or delirium occurring as a complication of it. Undoubtedly the most common acute infection which brings about delirium tremens is pneumonia. Krükenberg and Bonhoeffer found pneumonia in every seventh delirious patient. Jacobsohn in 281 delirious patients, found pneumonia in the ratio of one to eight; in 1,066 patients in Bellevue Hospital, pneumonia occurred in every fifth patient. Traumatism such as fracture of the ribs, legs, arms, and skull, very frequently caused an outbreak of delirium tremens, although the percentage in which these occurred is much less than the acute infections. In our experience it is a noticeable fact that severe dislocation at the shoulder or elbow is not so frequently followed by delirium tremens as fractures of the long bones. Bonhoeffer believes that injuries to the breathing apparatus are especially likely to be followed by an outbreak of delirium. Many others lay great stress on epilepsy as a causative factor in the outbreak of delirium tremens, but it is a question whether the epileptic seizure is not an expression of the same causative factor which later produces the delirium. An epileptic attack is given as the direct cause of the outbreak of the delirium in from 2.5 to 16 per cent. Among chronic alcoholics, epileptic attacks are very common and in the majority are not followed by an outbreak of delirium. It is difficult, therefore, to accept the view that these are the cause of delirium tremens, although one cannot deny that it is reasonable to suppose that the mental shock produced by them may at times be sufficient to accelerate the outbreak of an already developing delirium. The sudden withdrawal of alcohol in uncared for patients, in whom no attempt is made to replace it by proper treatment, is undoubtedly at times the cause of an outbreak of delirium tremens. This is due to the sudden change of the conditions of life, for when individuals are properly treated, the sudden withdrawal of alcohol does not produce delirium. That delirium tremens is caused by some factor outside of chronic alcoholism seems undoubtedly true but the definite specific cause is unknown.

Symptoms.—The outbreak of delirium tremens is never sudden; there are always premonitions. The patient becomes peevish, excitable and restless, loses sleep, and when he falls into slumber, is disturbed by dreams from which he starts in anxious fear. Beginning hallucinations appear which he recognizes as dreams, but although he knows they are unreal, they still disturb him. He often feels oppression around his heart which may increase to precordial pain; there is singing in his ears, which may develop into voices scolding, abusing or even threatening him; the dizziness increases; and tremor becomes more marked especially in the hands and tongue. This incubation period may extend over several days or, according to Kraft-Ebing, as long as twelve days. Where the delirium occurs in the course of pneumonia it appears generally on the third or fourth day, and, following an accident or fracture, usually on the second or third or may be delayed until the fifth or sixth day. The writer has seen it appear in twenty-four hours, following a severe stab wound in the abdomen. Many patients on the verge of an outbreak of delirium tremens will deny positively and firmly that they

have drunk any alcohol; when this is in marked contrast to the physical evidences of alcoholic indulgence it should always warn one of the imminence of a severe outbreak.

Many patients, when they begin to have insomnia and disturbed dreams at night, realize their condition and come to the hospital for treatment. They still know that the hallucinations of sight or hearing are dreams and explain this carefully. Some are still able to focus their attention on other matters and avoid the hallucinations that appear when dropping to sleep. One patient explained to me that he would read most of the night in order to avoid the family of skunks that came and played about his legs. They are often free from hallucinations during the day time and, after a few nights of disturbed slumber, improve, and this abortive form of delirium tremens passes over. In other patients, after the premonitory symptoms, the intensity suddenly increases and they are brought to the hospital in a furious and active delirium. This is usually connected with their daily occupation and they show no fear of what they see but are furiously belligerent; their attention can easily be obtained and they will explain minutely what they see, and demand to have their orders executed and explain logically why they wish to have this done. These patients, after a hypnotic and a night's rest, will clear up absolutely and by next morning remember shamefacedly what they had done. The delirium usually does not return.

The majority of patients, when the delirium is fully developed, appear severely ill with a disturbed and anxious countenance or their expression may be one of indifference; the face is congested, often slightly cyanotic and covered with sweat; they are restless, wandering about, busily twisting and turning, listening to imaginary voices and sounds. If in bed, they frequently attempt to leave it, pull and pick at the bed clothes, jump up, attempt to rush from the room and frequently hurl themselves against the walls to escape imaginary objects or push against the walls to prevent their falling in and crushing them. They fail to notice objects in their way and are indifferent to severe injuries. The gait is uncertain from the muscular tremor, which is noticeable in their hands with every movement, and often extends into the tongue and the muscles of the face. Their speech is trembling and stammering, or they blurt out expressions in short, sharp sentences. Some hardly speak at all; others shriek out questions and answer them, angrily discussing something and frequently scolding and cursing imaginary bystanders. The pulse is full, bounding and increased in frequency in the young and vigorous individuals and in the elderly or weak it often increases in frequency but is soft and weak. The respirations are increased, the tongue is usually coated, depending however on the condition of the stomach, for when the digestion remains good it is often clean, bright red and glazed; the temperature as a rule is near normal. By speaking sharply to the patient, his attention may be arrested for a moment and he may answer correctly the question put to him. It is evident that ordinarily the ideas of his personality and past remain clear; it is equally true that he has false ideas regarding his environment, the purpose for which he is in the hospital, the length of time that he has been there, and the individuals who are around him.

Hallucinations of sight predominate and it is usually an occupation delirium; for example, one market man had the entire field of vision filled with blue potatoes which rained incessantly down upon him; an hostler saw innumerable numbers of wagon-wheels rolling at him; the deck hand on a steam-boat begged me that he might go to bed as the room was rapidly filling with steam-boats that were bearing down upon him; the circus man saw elephants jutting out into the room, which crowded him, although they did not terrify him; the teamster usually drives horses and it is often a noticeable fact that as long as the horses obey his orders, he is not terrified, but if the horses back against his orders and he is unable to control them, there is instant terror inspired and the intensity of this is often a fair criterion of the severity of the delirium. The animal or menagerie delirium is common and the patients may see well known animals, or fantastic beasts and various horrid forms of monsters, or there may be disgusting insects, crabs and snakes of various forms or the animals they see may be of various abnormal colors, red and blue predominating, such as "pink giraffes that crossed a purple bridge and nibbled at his feet." These animals or imaginary monsters are not seen singly but usually in vast numbers. At times the hallucinations are pleasant and the room is filled with beautiful pictures; angels are seen talking to them, or God appears, talks to them, and commands them to go forth as his messenger. Sometimes the visions take on a sexual type. Various paræsthesias of the skin cause hallucinations of worms or spiders crawling on them. Specks on the walls or on the bedclothes, may be mistaken for various animals or vermin. Scratches, furuncles or injuries and the like may be mistaken for the bites of animals or for wounds given in attempts to murder them. The hallucinations of hearing consist of various noises, as the ringing of bells, crying of children, shrieks of people in distress, and volleys of musketry, or they are cursed and jeered at as traitors, murderers and thieves, or they hear their family outside the door conspiring to kill them or whispering and making plans to come in and mutilate them, often the mutilations taking the sexual characteristics. Rarely there are hallucinations of smell, and they imagine that the house is on fire, that smoke is coming up around their bed, or that sulphur fumes or other ill-smelling gases are being injected through the key-hole. The hallucinations of taste are also rare, but they may imagine that their food is covered with disgusting substances or that poison is being placed in it. The imperative monotone hallucinations are absent, although there is often rhythmical character to the aural hallucinations given by the ticking of a clock or dripping of water from the faucet, producing reflex ideas of speech hallucinations, usually of a scolding nature. Hypochondriacal illusions from sensations in the intestines, stomach, bladder, etc., do not occur; when these are present they give good cause for the suspicion of other mental diseases. Muscle and temperature sense are also normal.

The mental processes in delirium tremens are of a peculiar nature; there is no diminution in general in the sharpness of perception of the sense organs; the ability to recognize objects seems intact. Some authors however, believe that these patients are unable to obtain any sharp, clear impressions and explain the misinterpretation of noises, etc., as due

to disturbances of apprehension; these become very apparent when the patients attempt to read, when instead of correct sentences there is a senseless series of words and sound associations which is especially noticeable when the type is small and indistinct; sometimes there is no relation between the reading and the subject matter. Bonhoeffer's explanation that the inability to read accurately is due to disturbances of attention seems nearer the truth. He believes that the paraphasia and paralexia are closely related to the processes of physiological inattention. The power of attention under special conditions in delirium tremens can for a short space of time attain the sharpness of that in healthy persons, but the ability to hold the attention is quite different. The more complicated the mental work, the greater necessarily are the demands on the attention and the greater the tendency to paralexia. With a sharp strain on the attention for the purpose of holding fast this maximum accuracy of any sensory region, a transitory normal value is attained but there appears an increased tendency to hallucinations in the sensory regions. If the attention is held at a middle level but still so strongly taxed that the patient must talk with, and give answers to the examiner, the hallucinations become rarer as with all hallucinatory mental diseases. The disturbance then records itself in a tendency to mix up words and ideas similar to the physiological inattention. There exists in delirium tremens a persistent tendency to sink to a still lower level of attention.

Closely allied to changes in the ability of fixing the attention, is the train of thought by which stimuli through the various sense organs bring about the final conception of the object. Simple pictures presented to a delirious patient, or familiar sounds, may be often correctly recognized and designated, but in severe cases often these are misunderstood and cause hallucinations. At times the misinterpretation of pictures would lead one to believe that lack of color perception played a certain role. It is very characteristic for the misinterpretations to influence and lead to illusions through internal rather than through external similarity, as, for instance, the patient, looking at a picture of a bird, declares that it is a bird's nest. The final conception of the object lacks intensity and the ideas which come into consciousness are those which belong to associated related ideas. These patients are particularly susceptible to suggestion; this, however, extends only to the regions of sense from which the hallucinations come and it is therefore strongest in the optic and in the auditory senses but often fails with touch, and seems to completely fail in the regions of smell and taste. Suggestion can also affect the hallucinations concerning their external environment, especially as to occurrences in the recent past, but has no effect whatever upon the events of their early life. These patients have no idea of the passage of time and the duration of their illness is usually wrongly given; the day, the week, the year, are ordinarily misstated. The power of retention is much diminished and memory of objects seen is defective, this being strongest at the height of the delirium but also clearly apparent when the delirium has nearly ceased. The power to combine thoughts is distinctly in abeyance; this is clearly seen when one permits a patient to read, for he will read spontaneously the greatest nonsense without exerting the slightest critical faculty.

One of the most marked peculiarities is the misconception of place and environment and, up to a certain degree, of time; they have entirely lost their orientation. They are able to remember and describe clearly the contents of their own room; one can sometimes make them clearly appreciate the objects which compose their present environment, and yet they will be absolutely unable to appreciate that they are not in their own room and in a hospital. Their occupation, former life, and all ideas that relate to their personality, are unaffected. Ideas of grandeur do not occur in true delirium tremens; if they appear, it is the complication of some other psychosis. The emotional attitude of the patient depends largely upon the character of the hallucinations and illusions; they may be happy or fearful, they are more often anxious and fearful, and these may rapidly replace each other from time to time. The feeling of anxiety is almost never absent from the beginning of delirium tremens; it is first seen as an oppression in the chest or as an external restlessness; this feeling of anxiety or terror seems to be particularly prominent in patients with dyspnoea. During the height of the delirium the anxiety often diminishes and gives place to a euphoria, so that the patient becomes indifferent even to the hallucinations which previously terrified him, and he may even be amused at the external phantasies that are being worked out and played before him. The motor impulses are in most patients very pronounced. As many patients show occupation hallucinations in some degree, so their movements usually correspond with these. The impulse to speak often corresponds with these movements, but frequently patients will be busily moving about for hours, or lying in bed actively busy in many ways, without saying a word.

The tremor from which the disease really takes its name is apart from the motor impulse just described and differs from the ordinary tremor in chronic alcoholism only in its intensity and in the greater distribution. It may be so marked in delirium tremens that the patients totter and are unable to hold themselves erect, or, when lying in bed and suddenly spoken to, it may assume such convulsive intensity as to throw them off the bed. It persists even when the patients are at rest, although by movement there is a great intention increase. The tongue trembles strongly when thrust out and this often causes intense tremor in the muscles of the face. The eye muscles remain free from tremor and the head as a rule only takes part slightly. In slight degrees it can be controlled when the fingers are held closely together, but becomes distinctly apparent when they are stretched wide apart. In convalescents, after the tremor has disappeared, it can be felt in the interossei muscles when these are taken between the index finger and the thumb. The speech often shows a distinct ataxia; besides trembling of the voice, there is often also a stumbling over syllables and words, and mispronunciation, which is as apparent in voluntary speech as it is in reading aloud. The handwriting shows some disturbance; besides the tremor, words and syllables are left out and an inability to follow straight lines with the tumbling of words above or below each other is seen. Sometimes in the morning tremor of drunkards, a glass of alcohol will steady the hand, so that the handwriting becomes clearer.

There is a great tendency to sweating and often the slightest exertion brings on a profuse perspiration. The tendon reflexes are as a rule not changed. The sleeplessness continues throughout the entire extent of the delirium and ceases as the delirious period comes to an end. As has been said, the temperature usually rests near the normal line during the delirium; it is however, in some cases raised, usually not above 101° , except in patients in whom the motor impulses are very intense and there is a consequent incessant muscular movement. Under these conditions temperatures of 103° and 104° are not uncommon; temperatures of 105° from these causes are of serious prognostic significance. Magnan describes febrile delirium tremens as a special form of the disease but it would seem that he has classified as a special group the patients in whom the most intense motor symptoms are evident, and it would seem that they differ from the other forms of delirium tremens only in the intensity of the delirium or of the motor impulses produced by the vividness of their hallucinations. They differ only in degree, and not in kind, from other cases of delirium tremens. During the summer months, in periods of great heat in New York, it is noticeable that this form of febrile delirium is most common when the motor excitement is very intense. The patient may pass into a condition of heat stroke, the temperature may rise to 108° F., and the patient die.

During the delirium the pulse runs from 80 to 110 when the heart muscle is in fair condition. In patients showing much emotion or in those showing intense motor activity, the pulse is correspondingly increased. Its quality is usually soft, and according to Krückenberg, often dicrotic. Constipation is the rule. Several German observers lay great stress upon the frequency of albumen in the urine of delirium tremens patients, with no other signs of nephritis, which disappears after the delirium has ceased. This albumin appears in about half the cases in the beginning of the delirium, and in others on the second and third day, it is transitory and may cease a day or so before the delirium or it may last a day or two after the cessation, but as a rule, is small in amount. Leipmann found albumoses in about 15 per cent. of the delirious patients, and toward the end of the delirium, they are found in addition to the albumin. Microscopically the urine contains few formed contents, a few round epithelial cells and rarely hyaline casts. Bonhoeffer quotes Elsholz as having found in the examination of the blood an increase in the polynuclear leukocytes and a diminishing of the mononuclear, but no leukocytosis. In cases of severe delirium the eosinophiles were absent.

The duration of an attack in mild cases is two or three days; it averages probably three to five days and may continue for eight or ten days. The cessation of the delirium usually follows a deep sleep which may last uninterruptedly for twelve to thirty hours. Some authors describe this sleep as coming on in the midst of the delirium but it is usually preceded by a period of weariness and relative quiet. When the patient awakens from the critical sleep he is sensible, the hallucinations have gone and his orientation is usually complete; his mental condition however is not fully recovered; the power of retention is diminished and the ability to combine thoughts is distinctly diminished for a few days. The memory of the recent illness is never complete but it is accurate for the essentials; it is very rare

that complete forgetfulness occurs. As to the duration of his illness, the patient rarely has an accurate idea, deeming the time shorter than it really was. In general the emotional and fantastic occurrences are better remembered than the ordinary ones but, after four or five days, even these lose their distinctness. Often for several days therapeutic measures, which were necessary during the stage of delirium, are remembered and still misunderstood as forms of persecution. In old alcoholics, who have had previous attacks of delirium, there is at times a certain appreciation of the disease during the entire delirium and they also show a corresponding clearness as to its occurrences. On the other hand these same patients are very prone to consider hallucinations as realities and retain these misapprehensions for a long period. In not a few patients there is a recrudescence of the delirium for a few nights, while remaining free of it during the day; any unusual excitement producing mental exhaustion may often during the day time bring back some of the hallucinations.

Meningeal Symptoms, Serous Meningitis, "Wet Brain."—In all forms of chronic alcoholism, but especially following acute and chronic delirium, a condition develops which has rarely been noted and Dana is the only one who has deemed it worthy of mention. This is the alcoholic meningitis or serous meningitis, the so-called "wet brain." It occurs with relatively equal frequency in men and women. There is no true inflammatory process and the condition is called a meningitis from the excessive amount of fluid, but this is a transudate, and meningitis is a misnomer. The most probable cause seems to be the degeneration of the vessels, the paralysis of vasomotor control and the weakened condition of the heart. It usually follows an attack of delirium tremens, though it may develop in any chronic alcoholic after a debauch, without previous delirium. When it follows delirium tremens, the patient, after a few days of delirium, sinks slowly into a semi-coma. The delirium becomes of a low, muttering type, and the patient retains sufficient consciousness to have the delusions and hallucinations of sight and hearing. He is roused with difficulty, though he will still take food. The pulse is rapid, the temperature remains normal or is slightly raised, but seldom over a degree. The pupils are usually diminished in size. The skin is hyperæsthetic and pressure on the muscles of the arms and legs and over the abdomen, causes pain. Conjunctivitis and keratitis often develop. In some patients the condition slowly progresses for several days, in others the effusion increases rapidly, and they sink into a more profound coma from which they cannot be roused. The arms and legs become stiff, the reflexes are all exaggerated, the neck is stiff, slightly retracted, and attempts to move it cause pain. The abdomen is retracted and the skin and muscles are still hyperæsthetic. The lids are closed; the pupils are contracted and react slowly if at all. The tongue is dry and brown, and there is usually incontinence of feces and urine. The pulse is frequent and feeble, and the extremities are cold. He may continue in this condition for several days and gradually fade out, or improvement may slowly begin, the mind become clearer, the neck less rigid, the hyperæsthesia diminish, and recovery slowly take place. Often three or four weeks are required before the patient is really convalescent. Pneumonia, especially inhalation pneumonia, is apt to develop; the temperature may rise to 101°-104° F., and the patient dies. In 709 cases of delirium in Bellevue Hospital, New

York, this condition developed in 108 instances (15 per cent.); of these, 37 recovered and 71 died—a mortality of 65.7 per cent. The prognosis is always grave when the coma and rigidity have become well developed. Dana gives the stiffness of the neck as a useful prognostic criterion; if the patient has not a stiff neck he will recover, but when it comes on, the patient dies.

Prognosis.—The prognosis of delirium tremens depends greatly upon whether it is complicated by trauma or infectious diseases, especially pneumonia. Bonhoeffer gives 122 deaths, or a mortality of about 11 per cent. out of 1,077 cases; of these, 40 per cent. were caused by pneumonia, 17 per cent. by other acute pulmonary diseases, 4 per cent. by acute intestinal affections, 5 per cent. by burns and injuries of the body, 2 per cent. by erysipelas, while of the 32 per cent. remaining, autopsy showed no acute somatic affections, but a considerable number had clinical evidences of cardiac collapse and anatomically friable yellow-colored heart muscle. In his own uncomplicated cases, this author had scarcely a 1 per cent. death-rate. In 709 cases of delirium occurring in Bellevue Hospital, there were 143 deaths or about 20 per cent. Of these, 61 died of pneumonia, about 36 per cent. There were 125 cases of pneumonia in these 709 patients, and after deducting these in the 584 remaining, the death-rate was about 14 per cent. Of the 125 cases of pneumonia, 64 recovered, leaving a mortality of 48.8 per cent. In uncomplicated attacks in young individuals the prognosis is fairly good. In the beginning of any attack of delirium tremens a guarded prognosis should be given. If the delirium develops into a severe form and the motor symptoms are very intense, the prognosis is correspondingly grave. The so-called moderate drinkers, who develop delirium tremens after trauma, have a bad prognosis,—in the experience of the writer about 50 per cent. die. In true delirium tremens, as differentiated from acute alcoholic hallucinosis, the tendency to suicide is unusual. The changing character of the delirium prevents the fulfilment of any transitory morbid train of thought. The premonitory stage of delirium tremens, when there is great intensity of painful emotions, anxiety and unrest, is the time in which the tendency to suicide is most apt to develop. It is difficult in these early stages, to say whether the patient is developing true delirium tremens or an acute alcoholic hallucinosis, so that the statement that in true delirium tremens suicide is rare, remains true.

Treatment.—We must realize that there is no specific and treat it symptomatically. Most of these patients have been subsisting, often for long periods, on alcohol, with little or no food. We must also realize that the danger is not in the delirium but in the diseased condition of the heart muscle and vessels and that the gastric mucosa is in such a condition that substances given by mouth may remain unabsorbed for hours, and then suddenly be absorbed and the system be overwhelmed by the summation of accumulated doses. This has always seemed to the writer the reason of the increased death-rate under the old digitalis treatment. Many drugs have been vaunted as causing sleep and cutting short the delirium, but in a disease in which the critical cessation comes on with sleep, it is really impossible to say whether the sleep was coincident with the crisis or whether there was really any cause and effect in the administration of the given hypnotic. The question whether alcohol should be

withdrawn at once or continued is still a mooted point. It is the writer's belief, after trying both methods, basing his judgment on the treatment of several thousand patients by each, that alcohol should be absolutely withdrawn in all cases. First and foremost, all these patients must be treated from the standpoint of those having a degenerated heart muscle and they therefore should be stimulated with strychnine (gr. $\frac{1}{60}$ – $\frac{1}{30}$, gm. 0.001–0.002) every four hours or oftener or by caffeine or camphor, and these are best given hypodermically. Strong coffee or tea can be given in mild cases instead of the pure caffeine. The patient should be given a purgative such as compound cathartic pills, compound licorice powder, or calomel. In young, vigorous adults, without any appreciable change in their arteries, who have recently been drinking, an emetic such as copper or zinc sulphate is often an advantage. These should never be given in elderly persons or in those who appear old for their age.

In mild and abortive attacks a dose of a dram of paraldehyde, repeated if necessary in an hour, is all that is necessary to cause sleep from which the patients frequently awaken either clear-headed or with their delirium lessened. In the severer cases, the paraldehyde may be given in dram doses, at hour intervals, even up to three doses. Other hypnotics, such as sulphonal, trional, etc., have in the hands of the writer usually failed utterly except in the mildest cases. Opium should be resorted to only as a last resort and is especially contra-indicated with pronounced arteriosclerosis. Hyoscine, (gr. $\frac{1}{12}$, gm. 0.0005) and morphine (gr. $\frac{1}{8}$ – $\frac{1}{4}$, gm. 0.01–0.015) hypodermically, should only be given to young and vigorous individuals in whom the motor symptoms are especially marked. Hyoscine alone, tends to increase the delirium, especially in women. Often in the severest cases a mixture of hyoscine, gr. $\frac{1}{100}$ (gm. 0.0006) with apomorphine, gr. $\frac{1}{10}$ (gm. 0.006) and strychnine, gr. $\frac{1}{30}$ (gm. 0.002) will quiet them and give at least a few hours rest. Bromides are insufficient and in the hands of the writer have been practically useless. Chloral is one of the best drugs when properly administered; small doses are useless and Lancereaux claims that they even tend to excite these patients. When the heart is properly stimulated chloral hydrate does not have any deleterious effects. Lancereaux recommends thirty to sixty grain doses (gm. 2–4); the combination of chloral and morphine is especially advantageous in that smaller doses of each can be given and the mixture be more effective than either singly. The mixture of morphine, gr. $\frac{1}{8}$ (gm. 0.008), chloral, gr. 15–30 (gm. 1–2) with tincture of hyoscyamus, \mathfrak{zss} (2 Cc.) tincture of ginger, \mathfrak{mxx} (Cc. 0.6), and tincture of capsicum \mathfrak{miii} (Cc. 0.2), and water to \mathfrak{zss} (Cc. 15) is very effective and can be repeated at the end of an hour. These hypnotics, while causing sleep, do not necessarily cut short the delirium, but after a sleep of some hours, the delirium is often quieter and there is the further advantage of rest for the heart from the cessation of motor excitement. Of late years the writer has used ergot hypodermically in Livingston's solution, which is as follows: One dram of the solid extract of ergot is dissolved in an ounce of sterile water and three drops of chloroform and three grains of chloretone are added, and the solution filtered; this is sterile and should be given straight into the muscles in the gluteal region or in the deltoid. It should never be given subcutaneously; if carelessly given, it will produce painful spots. The administration of thirty drops of this solution, hypodermically,

every two to four hours, reduces the dilated bloodvessels, lessens the various congestions, and brings about a better equilibrium of the circulation. After it, there is a distinct tendency to a quieter delirium and less need of restraint; it reduces the tremor, less hypnotic is required, and it diminishes the tendency to "wet brain." The writer has never seen symptoms of ergotism although thirty minims of this solution were given every two hours for ten days or longer. As soon as patients awake they must be given food, best in the form of milk or milk and eggs. This should be given regularly every two or three hours during the delirium but if asleep they should not be awakened for any reason.

The treatment for the "wet brain" condition should be begun as soon as it is suspected. Strychnine, gr. $\frac{1}{60}$ to $\frac{1}{30}$, and ergot, thirty minims, both hypodermically, should be given every two hours, and caffeine and camphor are also of use. The patient should be carefully fed every two hours with milk, broth, and eggs, and thorough purging is advisable. Alcohol seems to increase the effusion and should not be given. During convalescence, however, a little alcohol in the form of egg-nog two or three times a day for a few days is often of benefit.

Bonhoeffer recommends that delirious patients should be placed for several hours in a warm bath at 95° to 97° F., and that an attendant should sit beside them so that when they attempt to get out of the bath, their attention can be diverted. He also recommends that one or two attendants should sit beside the delirious patients and keep them in bed, which is excellent treatment where there are many attendants and few patients, but where the reverse is true in a large, active service, restraint is often necessary. There is no question that these patients should be confined to bed through the entire delirious stage, as in the wilder delirium it is often necessary to restrain them by a sheet tied around their ankles and then tied to the foot of the bed, and by another sheet which goes from the bed up over one shoulder, down through the axilla, across the back to the opposite axilla, out across the shoulder, up to the bed; the wrists, when necessary, can be restrained by a muslin bandage wrapped around over cotton wool which thus prevents abrasions and holds them firmly; sometimes a folded sheet stretched across is sufficient to hold them in bed. The hot, stiff, canvass jacket is essentially bad, as it rigidly binds the patient and prevents the radiation of heat. The question of the isolation of these patients and the permitting them to wander about in a padded room is often brought up; young vigorous persons can be so treated for a few hours, provided the tremor is not too great and the delirium not so violent that they will do themselves injury. We have, moreover, always to consider sudden collapse, and the degree of cardiac degeneration cannot be accurately judged, so that on the whole, it would seem better to keep all patients in bed during their delirium and not to isolate them. In hospitals, the patients, although in open wards, are but little disturbed by their fellows, especially during their delirium, because they are too much occupied with their own hallucinations to pay attention to the disturbances caused by others.

During convalescence, stomachics such as capsicum, nux vomica, and ginger are useful; often a mixture of nux vomica, cinchona, and gentian is an excellent tonic. In the febrile cases of delirium tremens a cold bath is often necessary; the patients are placed on a rubber blanket in bed, and

cold water is slapped forcibly upon them from a whisk broom; the impact of the water takes the place of the physical rubbing in the cold bath. Warm packs have been recommended, but often the resistance made by the patient, and the excitement produced, do more harm than good. Usually eight or ten days after the patient has recovered from his delirium he is fit to go out, and in hospitals his treatment here ceases. If possible, they should go to some place where they may live in the open air with good food and have moderate outdoor exercise. Total abstinence from alcohol is their only hope for future health; for this reason it is inadvisable to give any medicine with alcohol in it. Tonics should be in solid form containing no alcohol.

ACUTE HALLUCINOSIS.

Acute hallucinosis of drunkards is sometimes called acute alcoholic hallucinosis, acute paranoia, or acute persecutory insanity. It is closely allied to delirium tremens, and there are cases which seem more like connecting links than belonging clearly to either one. The patients suffering from this form of alcoholic psychosis are usually younger than in delirium tremens and belong to the better educated classes, while delirium tremens is most common among those who perform manual labor. The tendency of this form of alcoholic psychosis to develop as a concomitant symptom of trauma, pneumonia, and other acute diseases, is not so great as delirium tremens. Acute gastric disturbances are the most commonly observed physical ailments connected with it and it frequently follows fright and intense anger. Patients have been known in whom one attack of delirium took the form of delirium tremens and another the form of acute hallucinosis.

Symptoms.—These patients show a predominance of the acoustic type of hallucination, although optic and tactile hallucinations are not infrequently present, but not as prominently as in delirium tremens. There is, in the beginning, the same irritability, easily excited condition, restlessness and undefined dread as in delirium tremens, but they often show a peculiar sensitiveness to ordinary noises; they are sleepless, their dreams are bad, and they start in their sleep, terrified by an unknown something. This unstable condition may persist for days and then become somewhat better, and a further debauch cause all the symptoms to return and go on rapidly into a full development of the complete psychosis. They are often troubled, at first, with noises in the ears, which develop into the hallucinations of singing, music, shooting, screaming, etc.; finally they are persistently followed by definite voices, which hold their attention constantly at high tension and compel their undivided attention. Frequently they are brought into the hospital by the police because they have fled from the persecution of these voices, or they go to their rooms and refuse to come out or allow any one to approach. In this early stage, suicide is very common, especially in those in whom the terror is highly developed. The voices are sharply localized, they accompany the patient from behind, creep up at him out of the floor, come to him from a hole in the wall, or seem to be persistently telephoning to him. When he strives to sleep, they come up out of the pillow, from under the bed, and they follow his every movement. These voices have a

definite character; they may be the voice of a man, woman, or child, or the clearly recognized voice of some friend, or they may be unmistakably not human, or the voices may seem human and speak in a foreign tongue. The rhythmical character of the hallucinations is quite common and sometimes the patient hears constant repetitions of the last word spoken to him, or the last thought which he has had. As he goes into the street the auditory hallucinations, as in delirium tremens, take on the abusive character, and he hears himself called by name with various epithets added, or accused of various criminal acts. Not infrequently, the patient hears every thought as it occurs to him, spoken out aloud, and he declares that he knows the very spot of the tongue out of which his thoughts are loudly spoken; frequently he hears every movement he makes commented upon by the voices.

Optic hallucinations are present but take a subordinate position; they frequently occur at night and often are the outlandish, terrifying, mixed-up pictures seen in delirium tremens. The sense of touch is less often involved and hallucinations of taste and smell are absent. These patients are not usually disturbed by sensations from the internal viscera; sometimes, however, they seem to form an unimportant part of the hallucinations. When these last sensory regions give predominant hallucinations, there is always a strong suspicion that we are not dealing with a pure alcoholic psychosis, but with a more serious condition. Frequently there is a suspiciously disturbing misconception of all acts that are performed by others in his presence; he believes that people moving in the street are running together to discuss him; he is suspicious of the patients in the hospital, believes that the motions made by the nurse in handing him his food prove that he is about to be poisoned and misinterprets all therapeutic measures. The idea of persecution does not go further back than the recent past; his persecutory system is superficial, changes during the disease, and often develops suddenly; ideas of grandeur are sometimes present.

Consciousness is not clouded, and they retain their power to combine thought and their powers of retention. Disturbances in the process of thought, as in delirium tremens, are not present. Most authors seem to believe that their orientation for place, as a rule, remains intact. In the patients who show a type of the disease tending toward the clinical picture of delirium tremens, there is sometimes disorientation especially in the beginning of the attack. Tremor of the hands and tongue, and gastritis, are usually present; the symptoms of neuritis are not uncommon, and other disturbances of chronic alcoholism, such as a tendency to perspire freely, etc., are common, although they are usually less marked than in delirium tremens, perhaps because this psychosis more often occurs in younger individuals. Bonhoeffer states that the albuminuria seen in delirium tremens was not found by him in these cases. The duration of this disease varies from a few days to weeks. Rarely does it continue more than two months, according to Bonhoeffer. As the patients improve, there are periods in which they seem to be free from hallucinations. Finally the voices in their ears are recognized as such and no longer produce the hallucinations. The various erroneous impressions improve coincidentally with the disappearance of the voices. Wernicke believes, however, that these patients go through a paranoiac stage in some hallu-

inations in which their systematized illusions persist; however this may be, this stage is evidently of short duration, because the accurate appreciation of their psychic condition often occurs with an astonishing rapidity. They remember their hallucinations and are often proud to write a description of them. Sometimes these patients go from these acute hallucinatory stages into a condition of chronic delirium. There are no known pathological lesions characteristic of this psychosis.

Prognosis.—The prognosis as to life, if they are put into an institution, is good, but if they go through the early stages uncared for, the danger of suicide is great. The liability to death from intercurrent disease is not great, and the more they tend in their clinical picture toward the transition type of delirium tremens, the shorter seems to be the duration of their delirium. Ideas of grandeur seem to tend to a somewhat longer duration. As in delirium tremens the same patient may show repeated attacks of this psychosis following continued excesses of chronic alcoholism. If the paranoiac condition has been prominent, continued alcoholic indulgence is liable to produce permanent insanity.

Diagnosis.—Bonhoeffer gives the following differential diagnosis between the acute hallucinosis and delirium tremens: The acoustic region dominates in the hallucinations in hallucinosis, the optic and tactile in delirium tremens; in hallucinosis orientation is retained, in delirium tremens it is lost; in hallucinosis the morbid occurrences are systematized and the patient has the illusions concerning his relations with others; both these conditions are lacking in delirium tremens; the disturbances of retention and the disturbances of memory dependent thereon concerning time and succession, the confabulation, the disturbances of attention and the power to combine thought are lacking in hallucinosis or at least are scarcely apparent. In spite of these differences, transitional forms occur which are likely to cause errors in diagnosis.

Treatment.—This is the same as for acute insanity; the tendency to suicide must never be forgotten and isolation is ever contra-indicated. They should be kept in bed during the delirium; hypnotics should be given to produce sleep as in delirium tremens; especial attention should be paid to their digestion and to frequent feeding; cathartics will usually be necessary. Bonhoeffer recommends frequent warm baths for these patients. One can often impress on them after their recovery, with much better hope of intelligent appreciation, the necessity of total abstinence from alcohol. We are dealing with patients, as a rule, more intelligent than those suffering from delirium tremens, and have therefore a better chance to make them appreciate their condition and the dangers of further indulgence; they are also often less injured by the lesions of chronic alcoholism.

CHRONIC ALCOHOLISM.

Many of the forms of chronic alcoholism are described under other diseases, such as cirrhosis of the liver, arteriosclerosis, etc., for here, as in all forms of alcoholism, the idiosyncrasies of the patient are important factors and the kind and amount of the alcohol used also modify the clinical picture.

The amount of alcohol which, consumed daily, will produce the lesions and symptoms of chronic alcoholism varies with the individual; most men who partake of moderate doses dilute their alcohol with large amounts of water and the effect produced is less than when the fluids are taken in concentrated forms. Many men take moderate amounts of whisky through long years with apparently no serious effects; many others partake of moderate amounts with their meals and seem to be benefited, and not injured, thereby. It is a noticeable fact that the wine connoisseur rarely becomes a drunkard. As soon as an individual begins to take alcohol for the effect produced, he is in danger of continuing the practice and becoming more and more tolerant; he requires more to produce the desired effect and soon partakes of amounts that necessarily must injure the organism.

When once the condition of chronic alcoholism is developed, the first symptoms are those of weakening of the will and blunting of the moral nature; the patients become untidy and slovenly in their personal habits; are careless in their ways of doing things; forgetful of their promises and engagements; lose their sense of responsibility to the community as citizens, and to care and provide for their families. They become more and more selfish and self-centred, increasingly incompetent through forgetfulness and carelessness, and to cover up their shortcomings are at first prone to make excuses which are followed by actual lies to escape the responsibility of their misdeeds. They lose their sense of shame and although, while the remnants of their better nature remain, they may promise to give up drinking, if they break this promise, they make excuses and seem to be shameless regarding it. They are irritable, touchy, and liable, from slight causes, to intense fits of anger during which they will cruelly punish their children for slight offenses; they may abusively scold their wives and families on the slightest pretext or brutally maltreat them. With the weakness of will there is a conceited self-complacency which causes them to declare that they can stop drinking at any time if they wish, and yet when pinned down to the necessity for so doing, they have a never-ending series of excuses to avoid doing it. There is a very characteristic suspicion in the minds of these patients of the faithlessness of their wives, which, according to Kraft-Ebing, is produced by a failing sexual desire and a rapidly occurring impotence. Usually this does not express itself further than in contemptible and vicious vituperations; it may cause, however, in fits of drunkenness, actual bodily harm and even murder of an innocent wife or of the children, as suspected accomplices of their mother. These evidences of mental degeneration may continue through years, and the patient finally sink into early senile dementia, for unfortunately a degenerated intellect does not necessarily produce death, and as long as the heart and arteries hold out, many degenerated alcoholics continue to live, a burden and nuisance to the community. They usually die before the alcoholic dementia is fully developed, because of their liability to trauma and intercurrent infectious diseases, or during an attack of delirium tremens or other psychosis, or from visceral degenerations, or cerebral hemorrhage.

DIPSOMANIA OR PERIODIC INEBRIETY.

In some individuals alcoholism exhibits itself in the form of periodical crises, the dipsomania or periodic inebriety of some authors. These patients are often total abstainers between attacks and struggle against the desire when it comes over them. Some authors believe these attacks are related to periodic epileptic explosions. Thélât defines the chronic alcoholic as one who becomes drunk whenever the opportunity is offered, and the dipsomaniac as one who becomes drunk only when the attack seizes him. Often these attacks are preceded by mental depression, restlessness, irritability, headache, anorexia, sleeplessness and precordial anxiety, and the desire to drink becomes irresistible. They will drink until the attack is past or until forced to desist by restraint. Some patients will mix various disgusting substances in their beverages, hoping thus to stop the craving. The periodicity varies from weeks to months or even a year or more. In some men regular recurring tasks or business stresses bring them on; in some women the menstrual periods seem to be the cause of the outbreaks. In others the attacks develop without apparent exciting causes. In some patients if protected for some hours or days, the craving passes away and they are safe until the next attack. In the beginning many patients drink only to drunkenness, but later their debauch goes on until they are forced to cease under restraint. In the majority, the periods between attacks shorten until they finally develop into the characteristic condition of chronic alcoholism, with no periodicity to their incessant indulgence. During their debauch they may develop an attack of delirium tremens or other forms of alcoholic psychosis.

ALCOHOLIC TRANCE, AUTOMATISM OR PATHOLOGICAL DRUNKENNESS.

In psychopathic, hysterical, or epileptic patients, or following traumatic injuries to the skull, or after sunstroke, alcohol produces disturbances of consciousness which deviate greatly from the ordinary sequences. The same conditions are seen in those who have been injured through the excessive use of alcohol; one of the simplest expressions of this condition is that in which the patients, after much smaller amounts of alcohol than formerly, become drunk and are absolutely oblivious next day to everything that occurs. After the first or second drink of whisky they may seem to their friends simply to have been drinking and not more than usual under the influence of alcohol, or they may in slightly more pronounced cases, completely lose their orientation, misinterpret entirely their environment, and show an ugly disposition, which was foreign to them, with evidences of a high degree of emotional anxiety. More pronounced examples of alcoholic automatism are those in which the patient may start off on a prolonged debauch and at the end wake up in some far away city and all occurrences from the time he began until coming to himself be an absolute blank. The amnesia is usually complete; sometimes there are faint recollections that he has been recently in certain places; for instance, one patient of the writer remembered taking a drink in Boston and ten days later, having gone through a five days' attack of

delirium tremens in Bellevue Hospital, came to himself with complete amnesia of everything which had occurred during the ten days; another who was drinking and sociably chatting with a friend, with no intention of taking enough alcohol to disturb his sobriety, came to himself five days later while ascending the stairs of a station of an elevated road, and was unable to remember any occurrences of those five days except that he had been in some bath establishment. This man was not an alcoholic, and filled a responsible position, although some years previously he had drunk to excess. Other patients, after a single drink or during a debauch, have been known to start off on long journeys and come to themselves on board a railroad train or a steamer. Others have been known to conduct complicated business transactions shrewdly and successfully, to go into court and conduct successfully a long trial, ending with a prolonged charge to the jury, come home and write out a long legal document concerning the case with perfect clearness and conciseness, and yet when consciousness returned, the amnesia was complete. In some this will occur but once, in others it is of recurrent nature and may be preceded by restlessness and irritability, and after a single drink they regularly go into this state of disassociation of consciousness. In these conditions men have committed forgery, theft, and even murder, without any recollection of them when consciousness returns, and are stricken with a deep remorse when accused of wrong-doing and made to suffer for their crimes. Others in this condition of pathological drunkenness will murder their children for trivial causes and show no remorse for the act; calmly deliver themselves up and discuss the whole occurrence with no more appreciation or mental disturbance at what they have done than if they had broken a piece of furniture or accidentally injured some animal. Many of these cases belong to medicolegal literature rather than to general medicine. There is no question as to the reality of the total amnesia in these cases, and the responsibility for their acts should be placed in the same category as those of the acutely insane.

ABSINTHISM.

Lancereaux described a special form of chronic alcoholism produced by excessive indulgence in absinthe, various liqueurs and aromatic essences. The substances in the absinthe of commerce he divides into two groups, the convulsive and the stupifying; in the first are absinthe, hyssop and sennel, and in the second annis, angelica, menthe and marjoram. Absinthe and annis produce the main symptoms. He divides the clinical manifestations into acute, chronic, and hereditary absinthism. The symptoms in acute absinthism come on suddenly; the patient becomes agitated, screams, loses consciousness and falls; there is a tonic convulsion tending to opisthotonos, followed by a succession of clonic convulsions for twenty or thirty seconds. He then falls back heavily, lies still for a few moments and regains consciousness. He has no recollection of what has occurred and is astonished that people should be caring for him; this lucid interval is of short duration and is succeeded by similar convulsions lasting for ten or twelve hours. In others the tonic convulsions are followed by clonic convulsions, and the patient throws himself from side to side, grinding his

teeth, screaming and foaming at the mouth, trying to bite those around him, striking his chest, and tearing at it. These attacks are of short duration and followed by a period of calm; they end suddenly without cyanosis or coma. A series of such convulsions leaves the patient weary and somewhat stupid. For a day or two he may feel the effect but at the end of this time he is entirely recovered. Acute poisoning of this kind is usually recovered from, although death may occur during the attack.

Chronic Absinthism.—The patient not only suffers from convulsive attacks, but also has neuritis and terrifying hallucinations. Chronic poisoning develops often from an indulgence of less than a year and from amounts of the liqueur which seem inadequate to account for the symptoms on the ground of the alcohol consumed. Women seem to suffer more frequently than men, and especially women below twenty-five years of age. These patients have morning vomiting and marked dizziness; there is marked irritability of the muscles; the eyes are fixed and brilliant; they sweat easily; tremor is marked; and there is extreme hyperalgesia of the body. There is marked hyperæsthesia of the skin over the exits of the spinal nerves, diminishing in intensity from below upward; the plantar reflexes are extremely active. Pressure on the abdominal wall is painful, and tickling or touching in the lightest way causes such agony that the patient screams with pain. The tenderest points are in the lower abdomen outside the recti muscles and out into the iliac fossæ. This is accompanied, especially at night, by the most intense pain in the muscles of the legs. In cases of long duration the hyperalgesia is succeeded by analgesia, but the pain, on pressure over the abdomen, chest, or the spinal column, remains almost as intense as at the beginning. These patients are sleepless or, when falling to sleep, are troubled with terrifying nightmares. Hallucinations of hearing are rare, but have a menacing character and are heard especially during the night; the mental ability, as in all alcoholics, shows weakness. One would judge that they lapsed rapidly into the chronic delirium and not infrequently died in this condition.

Hereditary absinthism is shown in children whose parents are addicted to its use. These children seem to possess an unusually unstable nervous system and are especially prone to convulsions in infancy, and later to hysterical manifestations, and convulsive seizures. It has been noticed in Bellevue Hospital during the past few years that patients, who give a history of drinking absinthe, have shown attacks of convulsions and in the majority there has been marked hyperæsthesia and hyperalgesia of the lower extremities; the extreme types as described above have not come under the writer's observation.

KORSAKOW'S PSYCHOSIS.

For many years there has been recognized among chronic alcoholics a condition of delirium combined with a polyneuritis; this was finally classed as a distinct and separate psychosis by Korsakow and is now generally called Korsakow's psychosis or syndrome. Mentally there is loss of orientation and a marked defect in the power of retention of new impressions, and loss of memory for the recent past and also for events during various periods of the patient's whole life. There is a strong tendency to

confabulation, and to fabrications of the most absurd character and even hallucinations, together with a polyneuritis. This usually occurs in the prime of life and is said by some authors to be more common among women than men, while the statistics of others show a preponderance of men over women. It usually follows excessive indulgence in alcohol for long periods, although it has also been described as occurring as a result of infectious diseases and following poisoning from lead and arsenic. In the majority of the patients the psychosis begins with the delirious stage and this may be so marked that at first a diagnosis of delirium tremens is made, but the critical sleep, so characteristic of delirium tremens, is absent and the delirium pursues a protracted course. Acute hallucinations fall into the background and the defects of mental retention with the lack of orientation of time and space, and the foolish babbling, become more pronounced. In other patients, and some claim this to be the usual course, there is a prodromal period during which there are signs of forgetfulness, mental aberrations and irritability; in some sleeplessness, and in others a stupor from which they are aroused with difficulty. The symptoms of neuritis may precede the delirium or not come on until after it. The length of this prodromal stage varies in different individuals. Bonhoeffer describes a form which develops as a very slow progressive weakness of memory with a sudden exacerbation of disturbances of memory to a definite standpoint. When however the characteristic delirium is developed, there is a distinct loss of memory for the recent past; events of their early life may be very clearly remembered, or up to a certain definite time. This amnesia may be complete or there may be curious lapses of memory in which the patient forgets some events and, without any apparent reason, remembers others which occurred during the same period. Many lose all orientation of time or space; especially is the time element defective; they cannot tell whether an event occurred a few moments or a week or several years ago. These gaps of memory are filled in with curious fabrications. This tendency to confabulate and indulge in pseudo-reminiscences is very characteristic of this psychosis.

The sense of recognition is much at fault; the patient does not know those about him, or remember his friends or even his nearest relatives. The attention is easily obtained but kept with difficulty. In the early stages, hallucinations, usually of sight, occur only at night but as the disease progresses they become more intense and may be present during the day. Optic and tactile hallucinations are most common; these may or may not be terrifying and may assume the fantastic forms seen in acute alcoholic delirium. If the delirious stage comes on early and quickly, these hallucinations are then prominent. The emotional condition of the patients varies; some are excited, even simulating a condition of paresis; others are depressed, having the self-accusations seen in melancholia; they are often anxious and disturbed and, later in the disease, are apt to be irritable, quarrelsome, or simply indifferent; in some there is a tendency to be silly and funny; they are at times childish and easily provoked to whining and crying; but in very severe cases they are practically emotionless. They are noticeably lacking in mental initiative and for this reason are very prone to soil themselves; here also weakness of the bodily muscles and the neuritis play a distinct part. They show a distinct power of combination of thought and, as far as the power of retention

permits, can reason correctly, especially in some purely intellectual matters.

The symptoms of neuritis are those which accompany polyneuritis; they have the various anæsthesias, paræsthesias, or hyperæsthesias; there is often an ataxic incoördination; their gait is frequently unstable and they walk with their feet far apart; the regular pains and sensitiveness to touch and muscular weakness are present; the patella reflexes are weak or absent; the joints are lax and the muscles soft; these neuritic symptoms are usually more pronounced in the lower extremities and when the paralysis becomes marked, an atrophy quickly follows; there may then be contractions and permanent deformities. Paralysis of the extensors is more frequent than of the flexors. In very severe cases the upper extremities are involved and one finds a radial, ulnar, or median paralysis. Some individual muscles may escape while others may be paralyzed. The sensory disturbances are variously distributed. One can seldom prove these in single nerves but can simply make out well-marked zones of analgesia and hyperæsthesia. Disturbances in the sense of position not infrequently occur; delayed reaction to pain has often been observed, ataxia of the upper extremities is often extremely marked. Severe tropic disturbances may occur. The cranial nerves may be affected. The vagi are not infrequently involved, causing cyanosis, tachycardia, and a peculiar dyspnoea which produces short-breathed speech. Double-sided paralysis of the recurrent laryngeal nerves has been observed, as also disturbances of swallowing and of movement of the tongue. Paralysis of the palate has been seen and paralysis of the external eye muscles, especially of the abducens, is especially frequent. Ptosis is rare; the inner eye muscles, however, function well or fairly well, but slow reaction to light has been several times observed; true nystagmus has also been noted and nystagmus-like twitchings are very frequently seen in the last stages of the disease.

Wernicke has described a cerebral psychosis with paralysis of the eye muscles which runs an acute and fatal course; this he called poli-encephalitis hemorrhagica superior. This disturbance of the eye muscles went on to complete paralysis. Wernicke believed this to be a separate psychosis and held that it was characteristic for the clinical picture of the disease to have an associated ocular paralysis, a progressive course, and a rapidly fatal ending. Observations have since shown that patients with this group of symptoms do not always die, and several recoveries have been reported. Bonhoeffer, after fully reviewing the subject, concludes that poli-encephalitis hemorrhagica superior is not a separate clinical entity but that the ophthalmoplegia is moderate in certain cases and is an unusually predominating symptom of a general disease, and he further shows that it is nearly related, if not identical, with Korsakow's psychosis.

The course of this psychosis is a protracted one; the first stage up to the full development of the mental symptoms continues for some weeks. The neuritis usually shows improvement before the mental symptoms, and in the course of several months may go on to full recovery, although in some there may be permanent atrophy and paralysis. The mental improvement does not run parallel with that of the neuritis but requires a longer time. The powers of retention seem to be the first to improve; then the orientation improves sufficiently for the patients to recognize where they are, and they begin to realize who the persons are with whom they

come in contact. The length of time during which this improvement occurs is a varying one; it may take months or years before complete orientation has been obtained. Some authors believe that complete restitution can occur; others deny it. Most observers are unwilling to commit themselves to a definite opinion in this regard. Even after apparent recovery, most patients show some weakness of retention and a forgetfulness which often prevents them taking up their former occupations. They are apt to have a distinct lack of initiative and show irritability and unstable emotions while, unless there is total abstinence from alcohol, they soon revert to their former condition. These patients are very apt to die in the delirious stage and in the severe attacks in which the mental symptoms are very pronounced, death is not often long delayed. There is great tendency to die of intercurrent diseases. The prognosis in all recent cases is doubtful and what is of especial importance, it depends upon the general condition of the patient and the state of his cardiac muscle. In the early stages the severer the delirium the worse the prognosis and when the neuritis extends to the cranial nerves it is especially unfavorable; thus, when the vagus is involved with tachycardia, dyspnoea and cyanosis, death very frequently occurs. The prognosis for final recovery, if they have passed the severe stages, should always be given with great reserve. Although they may recover a fair amount of physical vigor and of their former mentality, the chances are always in favor of more or less mental defect remaining.

The treatment is in general symptomatic. In the early stages they are best cared for in some institution. In the early months, even in the milder cases, rest in bed is necessary. The neuritis should be treated as any other polyneuritis. The mental symptoms can only be treated through improvement in the general condition. During the severe delirious stages hypnotics may be necessary; in the later stages the milder hypnotics are sufficient when any are needed at all. When their mental condition improves and they are able to be about, it is best to give them light and easy tasks, which is better than attempts to improve the mental state by especial exercises of an intellectual character. When one may be certain that they will receive good care at home and can be reasonably assured of their total abstinence, the patients may be allowed to return to their families.

In addition to the clinical forms of chronic alcoholism already described, there are other designations given to various mental states in which various symptoms predominate. Occasionally, in patients in whom excessive indulgence in alcohol, usually without food, has produced intense exhaustion with complete mental confusion, a state of amentia appears which simulates manic depressive insanity. Following an attack of delirium tremens or acute hallucinosis, some sink directly into a paranoic state or this less often develops primarily. The ideas of suspicion and jealousy greatly predominate. In most of these the delusions are predominantly sexual and early in the disease hyperæsthesia sexualis is not infrequently present. They have the alcoholic emotional instability and may be dangerous. Since alcoholic excesses are at times a symptom of paresis, the diagnosis of this condition from the pseudoparesis of alcoholism may be difficult. The ideas of grandeur, the mental stupidity, with failure of memory and judgment of the parietic, are present with alcoholic hallu-

inations and ideas of persecution and infidelity; though the development is gradual and the course protracted, it is not progressive. Often the course is the final differentiation. If a chronic alcoholic survives long enough, the last stage of many of the above mental states is early senility and alcoholic dementia. This often occurs without any previous delusions or distinctly insane stages and is the final result of the cerebral arteriosclerosis and atrophy of the cerebral tissues.

TREATMENT OF CHRONIC ALCOHOLISM.

It is not always possible to obtain an accurate history of the length of a debauch or its intensity. If one studies the tremors in connection with the condition of the tongue, in the experience of the writer a fairly good guess can be made which is sufficiently accurate to justify one in acting on the conclusions thus drawn. If the tongue is not coated and there is no tremor, the patient has been drinking about three or four days; if the tongue is moderately coated and there is no tremor, it means the debauch has lasted about five or six days; a heavily coated tongue and no tremor, about seven days; a moderately coated tongue and a slight tremor, about ten days; a heavily coated tongue and a marked tremor, about fourteen days; a moderately coated tongue with a very severe tremor, about three weeks; a fairly clean tongue and a very severe tremor, about a month; a bright red, glazed tongue and a severe tremor, from six weeks to three months. This is true of young men up to about forty-five years of age; after that the tremor comes on earlier and a two weeks' spree will give as much tremor in an elderly man as a month's spree in a young man. In women these rules are not accurate; the nervous system is affected more intensely and earlier, while gastritis comes on sooner. A week or ten days' spree brings usually an intense tremor and women will invariably endeavor to hide how much and how long they have been drinking.

The same treatment applies as for delirium tremens; if a young patient comes in the midst of his spree, an emetic is very efficient, but this should never be given in elderly persons or in those in whom we suspect the arteries may be atheromatous. Calomel (gr. v, gm. 0.3) with sodium bicarbonate (gr. 15, gm. 1) in single doses, or two compound cathartic pills, should be given as soon as the stomach has quieted down. If the patient should be in the midst of the spree and has recently taken alcohol, one or two drams of paraldehyde with a half ounce of whisky will often give him a restful sleep; this may be repeated in an hour if necessary but if he has not been drinking recently, paraldehyde alone should be given or the mixture of chloral, morphine, hyoscyamus, ginger and capsicum. Hypodermic injections of ergot are usually most efficient, lessen the tremors and take away the feeling of collapse and exhaustion which the withdrawal of alcohol produces. As in delirium tremens, the writer is firmly convinced that alcohol should be withdrawn immediately and absolutely; if they are collapsed a hypodermic of strychnine and doses of aromatic spirits of ammonia replace the alcohol. Furthermore, the withdrawal takes away the idea that alcohol is necessary or that they need it in any way, and this is an essential element to be thoroughly emphasized. When the patient awakes, stomachics, such as nux vomica,

ginger and capsicum, should be given with his food. During the first few days, liquor ammonia acetatis, in half ounce doses, every three hours, is often helpful. Sometimes, in very nervous patients, antipyrine (gr. v, gm. 0.3) with the acetate of ammonia will help greatly. If the patient is furiously and "fighting drunk," either from acute intoxication or at the end of a long spree, a hypodermic injection of apomorphine (gr. $\frac{1}{16}$, gm. 0.006) will quickly transform the most pugnacious into a limp and docile object. He can then be put to bed and in a few minutes will drop off to sleep with no other medication. This rarely causes vomiting unless the stomach is full; if this does occur, it is of no disadvantage. This is often the best means of saving further struggles and the writer has never seen any harm come from it.

If the patients have recovered from the debauch, the question arises as to the permanent cure; some may pull themselves together under exceptional circumstances; these are undoubtedly those in whom the alcohol has not produced serious cerebral changes, but it can be said that they belong to the curiosities of medicine and it is not to be expected of any one who has formed the alcoholic habit. Institutional treatment, by which the patient may be assured that he will be protected against himself, and cannot obtain any alcohol for a period of one or two years, where he can live out of doors and bring his body back into as healthy a state as possible with a chance for the brain to recover from the poisoning of the alcohol, offers the surest means of cure. This may sometimes be done at home, if the patient can be controlled and carefully guarded, but the influence must be strong indeed and appeal intensely to his moral nature to affect him. Taken all in all, the influence of religion has proved most effective for this but unfortunately it is not applicable in many cases. Most alcoholics are very open to suggestion and in a small number of cases, hypnotism seems to have been tried with success, but this more often fails than succeeds. Suggestion does come in play in institutions where several patients are endeavoring together to break themselves of the habit; the concerted effort helps materially to strengthen the weak wills of many of them. These patients and their families are prone to turn to advertised quackery and nostrums to obtain a cure rather than to persuade the patient to put himself under regular restraint. The fact that legally in this country an alcoholic can not be restrained against his will often adds to the difficulty of doing anything that will really assist him. A treatment has been published by McBride of Toronto, which has proved very successful in his hands. The writer has tried it in a few patients and so far the results have been all that could be desired. It is as follows: As soon as the patient is over the severe effects of his debauch or if he is steadily drinking without any drunken outbreak, he should be given, hypodermically, three times a day, atropine and strychnine, of each gr. $\frac{1}{160}$ (gm. 0.0006); these drugs should be gradually increased until the full physiological effect of the atropine is obtained and the patient is taking a thirtieth or even a twentieth of a grain of strychnine, three times a day; when the mouth is continually dry and the pupils dilated, the atropine should be reduced slightly and held at this dosage for four or five days; then both the strychnine and atropine should be gradually reduced, and finally the patient should be given the drug twice daily, then once a day, and then

cut off entirely; the length of time required for this treatment is about a month or six weeks. Often the compound tincture of cinchona is added, especially in the morning when the craving for alcohol is the greatest. It is a noticeable fact that after a few days, usually in less than a week, the desire for alcohol has ceased, and the thirst from the dryness of the mouth is easily satisfied with water. McBride reports that he has tried this for a number of years and the patients whom he thus treated ten or twelve years ago have remained abstinent; this has not been universally successful but in his hands it has succeeded in such a large majority that it is worthy of the most extensive trial and it has the special advantage that the patients need not be confined or absent from their homes or even daily work.

CHAPTER X.

OPIUM. MORPHINISM. COCAINE.

By ALEXANDER LAMBERT, M.D.

OPIUM.

Historical.—There are many legends connected with the discovery of the effect of opium. Along the Nile its use dates back to very ancient times as the Egyptian hieroglyphics seem to show. Homer mentions the poppy as a garden plant; the ancient Greeks knew the means by which the narcotic properties could be obtained from the plant as appears from the writings of Dioscorides, and in some parts of India and Persia to-day the opium is obtained from the poppy by the same method that was described eighteen hundred years ago. Hippocrates is among the first in whose writings we find the drug recommended for internal use. The Egyptian priests used it as a nervous sedative, believing that the sleep produced gave opportunities for the soul to commune with the gods. The Arabian physicians were the first to study its value in disease and they seem to have made wide use of the drug. The Persians early recognized the opium habit, for they had a proverb that, although opium cured disease, it also produced a disease. Serturner, an apothecary in Germany, seems to have been the first to study scientifically the alkaloids of opium. Derosne, in 1803, discovered narcotin which he called the salt of opium, believing it to be the active principle. Robequet showed this belief to be erroneous and gave the name narcotin to this alkaloid. In 1804, Seguin isolated a crystalline body which has proven to be the narcotic principle but he did not seem to realize the importance of his discovery and, in 1817, Serturner again published the existence of a salt of opium, which he named morphi-um. Crothers says that, although opium has been used subcutaneously for a long time, morphia seems first to have been thus used in this country by Drs Isaac Taylor and Washington, in New York, in 1839, and its use abroad was not generalized until a syringe was introduced into the French army, in 1866, by Pravaz. The dangers of morphinism as a habit seem first to have been realized, in England, about 1864. Nausbaum in the same year drew attention, in Germany, to the injurious effects of its continued use. Since then the attention of the medical profession has been drawn more and more strongly to the increasing dangers of morphia and opium addiction. Not infrequently have physicians, in their efforts to relieve pain, been unconsciously responsible for the spread of this habit, and it is only in recent years that the full realization of this danger has become widespread. The pernicious habit of giving a hypodermic syringe to patients, teaching them to use morphia to alleviate a passing pain, has been all too frequent, and has been the cause of many an unhappy addiction.

Etiology.—The more highly cultivated and mentally developed a race becomes, the more intolerant is it of pain. This is especially true of the male sex. The Eastern nations have long used opium, thus in India and China, opium, though a curse from its excessive use, seems to be more often used in moderation without producing the same deleterious effects as in other races. This is not true of all Eastern races, for the Burmese rapidly deteriorate under its use. The great majority of morphia addicts are among the educated classes, especially those who deal continually with it, as druggists, physicians and professional nurses, and among these, men predominate. A large class are those who are neurotic from inheritance; their will and judgment are in unstable equilibrium and they are either dominated by a desire to gratify any momentary pleasure, or they seek comfort in anything that seems to stimulate and increase their mental vigor for the time being. They are often the children of alcoholic, tuberculous, syphilitic, or neurotic individuals, and unfortunately the alcoholism in the parent need not be more than the so-called moderation. Many persons of unusual intellect, precocious in early life, are pushed beyond their strength, mature early, and break under the undue strain. These seek relief from exhaustion by means of drugs and alcohol. It is not uncommon to find strong and vigorous men, after some severe shock or disappointment or after intense strain, given morphia to alleviate insomnia, soon becoming addicted to its use. Many patients, suffering from chronic and painful affections or incurable disease, become addicted to the use of morphia from the necessity of alleviating pain. Women suffering from disorders of the genital organs fall easy victims, and it is especially dangerous to prescribe morphia for women at the climacteric period. Formerly many patients became addicted to morphia through the widespread custom of giving it to relieve pain following surgical operations, but the number of these is enormously diminished since the danger has been recognized by surgeons.

Among Western nations the opium habit is indulged in more by the taking of morphia by mouth or hypodermically, or by drinking laudanum or paregoric, than by the smoking of opium. Among Eastern nations the smoking of opium seems rather to predominate. Of late years codein and heroin addictions have been recorded. Compared with alcohol, opium may be said to be equally degrading and destructive of the moral side of the individual, but it does not leave behind it the same amount of organic lesions in the individual nor transform the individual into the same vicious, destructive, and abusive beast that alcohol does.

ACUTE OPIUM POISONING.

Symptoms.—The symptoms of acute opium poisoning require little detailed description; the infrequent, stertorous breathing, the livid cyanotic appearance, the pin-point pupils, the cool, sweating skin, give a well-known and easily recognizable clinical picture. The respirations may simply be infrequent with a rythmical regularity or they may be in groups of three or four with many seconds between each group.

Treatment.—The treatment is chiefly a struggle to keep up the working of the paralyzed respiratory centre. The old method of walking a

patient up and down, injecting large doses of atropine to stimulate the respiratory centre and slapping him with wet towels, has always seemed to the writer ill-advised. The incessant walking up and down, staggering forward and back half asleep, exhausts the patient thoroughly and the liability to give, what is for that patient, an overdose of atropine and thereby add its poisonous effects, appears to be a dangerous procedure. One may see patients, brought to the hospital with their hearts very rapid from an overdose of atropine, die suddenly in collapse; they really died from the antidote and not from the opium. The slapping with wet towels soaks them with cold water and in the exhausted condition there is a strong liability that pneumonia may follow. It seems wiser to save the strength of the patient and the energies of the attendants for the long and tedious period through which artificial respiration must be kept up. As soon as possible the stomach must be washed out with a solution of potassium permanganate (1 to 500); a certain amount of this should be left in the stomach; whether opium be taken by the mouth or as morphia, hypodermically, the morphia itself is excreted into the stomach cavity and is then reabsorbed. It has been proven experimentally on dogs that more than half of the morphia given subcutaneously can be recovered by simply washing out the stomach. Dr. Moor, of New York, has shown that permanganate of potassium prevents the toxic action of morphia. In opium or morphia poisoning it is therefore wise to wash out the stomach at least every hour and leave a little of the permanganate solution in the stomach to destroy any of the alkaloid that may be excreted by the gastric mucosa. In the periods between washings a strong infusion of coffee should be injected into the bowel. Artificial respiration should be kept up until the patient is able, when left alone, to breathe eight or ten times a minute. This may mean many hours of hard and tedious exertion, but as long as the heart is beating, if respirations are kept up, there is a possibility of recovery. To relieve the cerebral venous congestion produced by opium, the injection of ergot hypodermically, as described under alcoholism, is most effective and satisfactory. It equalizes the circulation and relieves the congestion.

OPIUM SMOKING.

The smoking of opium is an ancient vice. It is claimed that this habit came from Egypt and Arabia to India, but this seems doubtful. At all events, it is mentioned by Barbosa as being found in India as early as 1511; from India it was introduced into China and is the chief method in this last country by which opium is used. In 1773, the East India Company first began the exportation of opium from India to China, following the Portuguese by a few years. Since 1860, the importation of opium into China, and the cultivation of the poppy, have greatly increased. Opium is smoked from a special pipe, the stem of which is usually twenty-four inches long, generally made of bamboo, at the lower third of which there is placed a bowl, usually of red clay, through which a minute hole runs down into the stem.

Compared with the other forms of opium addiction, according to Kane, smoking takes longer to form a real habit, works less physical and mental injury when once formed, and is easier to cure. A gradual rise in the

amount used is necessary in order to get the desired effect; the early pleasurable symptoms soon disappear and the evil effects on mind and body are similar in many respects and the symptoms incident to abstinence are the same. In smoking opium, the morphia is not all consumed and a large amount remains in the ash. Amounts of opium are smoked which, if taken by the stomach, would certainly produce death. Kane quotes the case of a man who broke the habit after consuming as a daily dose 594 grains. He gives the tabulated statement of the daily dose of 1,000 Chinese smokers; 646 varied between 16 and 128 grains; 250 from 160 to 320 grains; 104 from 480 to 1,600 grains. To obtain the desired effect 5 grains seem sufficient for a novice, while old smokers need as high as 290 grains. The average American seems to consume more than the average Chinaman to obtain the desired effect. This vice among Americans is of relatively recent origin, having been first taken up in this country in 1868, in San Francisco; from that time it rapidly spread through the west and from there to the east, until now, throughout the United States, it is by no means rare. Opium smoking is not confined to any one special class. It has among its addicts the wealthy of both sexes, the sporting man, the mechanic, and the dissolute. Neither all Chinamen nor all Americans who smoke, do so to excess; some, especially the former, do so but once a week, and persons are met with who smoke for months without forming any habit and without any apparent injury. The effect desired by the opium smoker is not that of slumber filled with fascinating dreams, but a condition of dreamy wakefulness in which the mind is lifted out of the petty annoyances and cares of life.

Symptoms.—The effect of opium smoking on a novice is described by Kane, who tried it himself and experimented with two other men; the first effect was nausea and dizziness, accompanied by a pleasant sensation of exhilaration, followed by a quiet, easy contentment; this was after deeply inhaling four pipes; there was an increase in the force and frequency of the pulse from 80 to 110, hot flashes over the body and face, and after a few more pipes came a soft pulse, lessened in frequency, and a fall in temperature, giddiness, and slight nausea, with some staggering on rising or walking, profuse perspiration, ringing in the ears, and intense itching over the entire body. The profuse perspiration and nausea continued, followed shortly by abundant and easy vomiting; there was also a feeling of uncertainty in putting down the feet in walking, sleepiness, heaviness of the eyelids, contraction of the pupils, dryness of the throat, and a fear of crossing the street if a wagon or car was approaching. The sexual appetite was increased. This was followed by intense sleepiness. The doze, however, lasted but a moment, the awakening being sudden; there were no dreams. The nausea was a prominent and distressing symptom and, in his case, lasted for twenty-four hours as did also the itching. The pulse dropped below sixty, and once, after ten pipes were smoked fell as low as forty-one, and remained so for six hours. Sometimes the novice does not feel at all sleepy and becomes very talkative even after the tenth pipe, and later, when desiring to sleep, although sleepy, he is unable to do so from intense fear that some catastrophe may occur. Among other novices the drowsiness may come on after four or five pipes, and they sink back into a heavy slumber, lasting for some hours. Twenty-four hours after smoking, the novice frequently feels languid, is without

appetite, has an intense headache, and the itching continues. Old smokers do not, as is usually believed, smoke a few pipefuls and then fall into a heavy sleep; as experience grows into a habit, stupefaction is less speedy, and it may require many hours and many pipes before even the coveted excitation is reached, and the majority complain that they are sleeping less than usual and are troubled by distressing insomnia. If the smoker has gone to excess, sleep filled with horrible hallucinations or a condition of terrifying wakefulness may follow. The stupid, sleepy condition of the next day is removed by a further resort to the pipe. The habitual smokers, who do not use the drug to excess, claim that, unlike any other form of opium taking, a headache never follows.

The effect of opium smoking is first seen upon the mind. The feelings of pleasant exhilaration and contented indifference are gradually more difficult to obtain and, after from three months to a year, they cease to occur although the amount of opium smoked be largely increased. If the addictee endeavors now to break it off, distressing symptoms show themselves so intensely that he is forced to continue. The continuance of the smoking brings with it a disinclination for continued mental effort, a weakness of the will-power, a lack of decision, and a loss of memory. A certain indecision, manifested by mental perplexity and impatience concerning the smallest actions, is often noticed after smoking. Dull mental hebetude often alternates with outbursts of violent anger, or there is a gloomy presentiment of impending evil only allayed when indulging in a pipe. During these periods of despondency, suicide, especially in women, is not uncommon. Neuralgias, noticed in other forms of opium taking, are rare during opium smoking. Occasionally colic is complained of but this seems more due to intestinal disturbances than to a direct effect on the nervous system. Tremor of isolated muscles sometimes occurs, but a general tremor, most marked in the hands and tongue, is noticed when smoking is excessive. The pupils, as a rule, are evenly contracted. When the effect of the last dose has worn off, the pupils are often widely dilated, and conjunctivitis, with burning and excessive lachrymation, is common. All who have smoked for any length of time, complain that they are getting near-sighted. The pulse-rate is usually above normal, except that after excessive smoking it falls below the normal rate. The flushing of the face with profuse perspiration in a novice, is replaced, in the old smoker, by a sallow and deathly hue. When under the full effect of the opium, the respiratory rate is lower, and prolonged smoking produces a chronic bronchitis with cough, and pharyngeal and laryngeal catarrh with loss of power in the vocal cords. In the alimentary tract there is gastritis and constipation, often accompanied by hæmorrhoids and an obstinate pruritus. The constipation is at times succeeded by a violent diarrhoea, which may become chronic and last for months.

The vomiting that attacks the novice may be only slight, come on suddenly and unexpectedly, and consist in a simple and spasmodic emptying of the stomach; later there may be persistent and violent attacks in which finally nothing but blood-stained mucus can be raised. The itching of the skin varies with the individual; in some it is slight and in others intense, especially in the genital region, so that they often excoriate themselves. The average specific gravity of the urine is low,

from 1,004 to 1,016; the reaction is usually neutral; there is an increase in the earthy and alkaline phosphates, and in twenty examinations Kane found no albumen, sugar, nor casts. For the first few months of smoking, in both sexes there is an increased sexual desire which is especially marked in young women, and opium smoking has been used as a means of seduction. After a few months there is a diminution of desire and impotence in the male. In the majority of women menstruation is not interfered with, although in some it is scanty and irregular and there may be amenorrhœa. In this, opium smoking differs materially from morphia addiction. Some women, who smoke excessively, habitually miscarry; in others it seems to have no effect whatever upon their pregnancy, and the children of some opium smokers, as far as can be learned, seem strong and healthy; this is again in opposition to the other methods of taking opium.

The symptoms of abstinence and the sudden cessation of opium smoking are the same in most respects as those which follow the withdrawal of other forms of opium, but the smoker often suffers less severely and for a shorter time than the opium eater or the morphia addict. The respiratory tract and the eyes are affected out of proportion to the rest of the body. The first symptoms are gaping, yawning, sneezing, profuse discharge of tears and mucus from the eyes and nose, irregularity of the pupils, ringing in the ears, followed by extreme restlessness, intense pain in the joints, nausea, vomiting, and purging; the vomiting and purging may become almost constant. A peculiar dull, drawing, dry, and burning ache in the pharynx and larynx occurs, which is followed by distressing tearing pains in the muscles, especially in the calves of the legs and between the shoulders. Chills, followed by flashes of heat, are felt along the spine and are followed by profuse perspiration. In some cases, if no opiate is used, the vomiting and diarrhœa continue and the restlessness and flushed face give place to complete relaxation, a ghastly pallor with sunken eyes, collapse, and death; but in less severe cases or when proper remedies are used, the distressing or dangerous symptoms cease one by one. Sleeplessness persists for a long time; the bronchitis and catarrhal inflammations of the throat usually last for months; the pains in the legs and body gradually disappear; the sexual power returns; the appetite gradually improves and becomes ravenous; an increase in the weight is manifested; a return to natural buoyancy of mind begins, and the patient regains his health and strength. Under proper treatment these symptoms can be cut short and the sufferings much reduced, but it is rare for individuals by themselves to carry out a cure to a successful issue. When once cured, it is difficult to say what proportion relapse, but a single indulgence may be sufficient to start them again into the habit. Rarely, individuals are found, who once having broken the habit, return to it and smoke but one pipe a week and do so for years without apparent injury.

OPIUM BY MOUTH.

This is much more widespread in this country than is generally realized. Dr. A. P. Grinnell recently ascertained the amount of opium, paregoric,

and laudanum, sold by the various druggists in a single month in sixty-nine towns in the State of Vermont. The figures show that the amount consumed would be sufficient to average a dose to every man, woman, and child, in the State of Vermont, every day in the year. By a dose is meant, 1 grain of opium, $\frac{1}{2}$ grain of morphia, $\frac{1}{2}$ ounce of paregoric and 20 drops of laudanum. Probably the most of the opium takers are those suffering from rheumatism, neuralgias, migraine, hepatic or renal colic, dysmenorrhœa or other troubles which at first caused only a temporary indulgence in the drug. Later, however, especially in elderly people, the habit is insidiously formed. Opium is often used at intervals for insomnia or to allay grief and mental suffering. It is given up when the strain is past, and taken up again for any reason that seems sufficient. Often in these cases the only symptoms seem to be a mental and physical restlessness and anorexia, with a disposition to sleep. The opium taker shows certain differences from the individual taking morphia. There is more excitement and exaltation following morphia, while with opium there is more a feeling of quiet contentment, lasting over a long time. The morphinist, after the feeling of satisfaction has worn off, is more apt to dread the slavery of his habit, while the opium taker never seems fully conscious of the danger. The opium taker rarely consumes as much as the morphinist and the duration of his existence, after the habit is once formed, is usually much longer. He may indulge for a year or more without apparent injury, but the morphinist, in a relatively short time, shows evidences of his degeneration and succumbs quicker.

Gradually the effects of the opium begin to show when used to excess. There is a change in the disposition; they become irritable, peevish, somnolent and show evident dishonesty in little matters, especially concerning the use or the procuring of the drug. They are prone to develop a sallow parchment-like complexion, although in the early stages their faces may be flushed, with a tendency to cutaneous eruptions, and this last condition of the skin is apt to persist; the hair tends to become gray early and they have an old, worn-out, exhausted, or cachectic appearance. There is often general feebleness of the muscular system with tremors, and this may be so pronounced as to resemble ataxia. The visions so vividly depicted by De Quincey do not seem to occur among western nations. Sometimes the imagination seems stimulated for a while, producing a dreamy, visionary state, but it is extremely doubtful if, under the influence of opium, the mind is capable of more intellectual vigor. No new thoughts arise, no new levels of intellectual ability are reached, and there develops simply a dreamy selfishness, producing an inclination to live apart from others, and to shun companionship. There is a tendency to ignore, and to break, appointments and social engagements. If the opium taker is found in company, it is usually among those who are below him in intellectual and moral development. His self-respect is gone, he is careless of his appearance, indolent in his habits, and neglectful of the decencies of life. In the end he sleeps poorly, grows emaciated, his eye becomes lustreless, and he goes about shrinking and cringing. In the later stages cardiac degeneration is prone to occur with attacks of pseudo-angina pectoris or with precordial anxiety; constipation is common, and the general nutrition is much disturbed. They are prone to die suddenly

from acute infections as erysipelas or pneumonia, or tend to go into melancholia or dementia.

MORPHINISM.

Indulgence in morphia is a vice of recent years; it has taken the place, especially in large cities, of the preparations of crude opium. The readiness and cheapness with which morphia can be obtained and the ease with which hypodermic syringes can be bought, have made this vice a widespread curse. Physicians, nurses, pharmacists, form, unfortunately, a large percentage of the morphia addicts. Rodet, in Paris, in 650 men addicted to morphia, found 40 per cent. physicians, 3 per cent. students in medicine, 3 per cent. pharmacists, 15 per cent. idlers living on their incomes, 8 per cent. merchants, 7 per cent. officers in the army, 5 per cent. workmen, and the rest scattered through many occupations. In 350 women, 43 per cent. were without occupation, 14 per cent. were prostitutes, 13 per cent. were working women, 10 per cent. were wives of physicians, and the others were scattered through various employments. As regards age, Rodet found in 324 cases that between twenty-five and forty the greatest number (60 per cent.) occurred; below twenty-five, 11 per cent.; from forty to fifty, 13 per cent. and the remainder after sixty years of age. Rodet also tabulated the maximum daily dose of 569 addicts; 25 per cent. took from 50 centigrams to a gram ($7\frac{1}{2}$ to 15 grains); 8 per cent. took below 10 centigrams, that is, less than 2 grains; 15 per cent. from 10 to 30 centigrams; 14 per cent. from 30 to 50 centigrams; 12 per cent. from 1 full gram to $1\frac{1}{2}$ grams; 10 per cent. from $1\frac{1}{2}$ grams to 2 grams, and 9 per cent. from 2 to 3 grams; the proportion rapidly diminished above this amount, there being individuals on record, however, who took from 9 to 12 grams a day. In studying the duration of the habit, Rodet found that in 270 individuals, 41 per cent. showed a duration of from two to four years; on the other hand, there were individuals who had been addicted to the habit for ten, twenty, thirty, and even forty years.

There are no pathological lesions which are characteristic of chronic morphia poisoning. Fatty degeneration of the heart muscle has been described and Schweneger has found hypertrophy of the left ventricle and dilatation of the right ventricle and pulmonary artery. Fatty degeneration of the liver is reported as occurring in a marked degree in those dying of chronic morphinism. These various lesions can not be considered as characteristic. The cause for which morphia is taken often modifies the habit which sooner or later is acquired; thus those who take it to soothe the agony of some chronic disease probably resist longest its baneful effects. Many who take it only to assuage pain, knowing full well the habit and its effects, often bear moderate pain without turning to morphia for aid and only use it when the pain becomes almost unbearable. The dosage in these patients is increased only as the need demands, and often the same dose will suffice for many months or years. In the end, many of these show the symptoms of chronic morphinism, but French writers differentiate this class of patients from those who take morphia for pleasure, in whom the habit

rapidly grows, and the demand becomes more and more urgent with increase in the dosage. These authors designate the first class as morphinists and the second class as morphinomaniacs. The question may arise in the case of a patient suffering from a painful and incurable disease, whether a physician is justified in giving morphia, knowing that if once used it must be given for the remainder of the patient's life. People are often opposed to having it said that members of their family died with the morphia habit. In many cases it is simply cruelty to refuse to give it, and, under certain circumstances, the formation of the habit in some sufferers is of absolutely no consequence.

The hypodermic use of morphia is the most seductive form of the habit and the hardest to break; some patients seem to require the sensation of the needle thrust in order to be satisfied. What is sought in most cases is the feeling of exaltation, strength, and mental vigor, with relief from pain or ennui, the drowning of sorrow, or the killing of the hopeless realization of despair and failure. Morphia does this as long as the desired effect lasts. The duration of this varies in different individuals and is longer in the beginning because the toleration for the drug is rapidly acquired and the time between doses must be continually shortened or the dosage increased, and finally both of these means must be used to obtain the desired results. In many who take enormous doses it would seem that all the morphia does not act, but some must remain inert and be excreted without action.

In the morphia addict there are practically three stages which, although shading into each other, can still be recognized; exaltation, intoxication and cachexia. The first is one of enjoyment, happiness, and satisfaction. When the effect has subsided it is followed by malaise, a feeling of restiveness, and painful anxiety, which a renewal of the dose takes away. The effects of a single dose will sometimes last for twenty-four hours, but this is soon reduced to twelve, then to six, then to three hours, then to minutes instead of hours, and finally, the exaltation ceases, and he must take the drug to quiet the intense craving and the pains of abstinence. When the period of intoxication is reached, a dryness of the mouth, nausea, and anorexia supervene. The habitué then notices that an injection taken just at meal time will give him the appetite which he lacks. The voice becomes hoarse, and singers can no longer use their voices. Digestive troubles appear; constipation is obstinate; there is a loss of sexual desire, and amenorrhœa in women. The memory begins to be treacherous; insomnia becomes marked; the patient passes his nights reading, although worn out with fatigue, and if he sleeps, it is not a refreshing slumber. In the daytime he is peevish from fatigue, ill-humored, and seems stupified and benumbed. He takes no interest in anything which does not pertain to himself, and his character is noticeably changed. There is moral inertia, absence of will-power, and complete self-centred selfishness. The nights become more and more dreaded, and soon, if he sleeps at all, he wakes constantly from his nightmares, which become more terrifying, and always of a distressing nature. His hair begins to fall out, the teeth to decay, and the body to emaciate. The face is drawn and aged; the eyes are lustreless, and the breath foul. Even from this stage it is possible to recover. If he goes on, the cachexia develops, emaciation becomes extreme, and the

secretions are practically suppressed; cedema of the legs appears and the slightest exertion causes oppression and a sense of constriction in the chest. The pulse becomes small and irregular. The heart's action is enfeebled; there is increased precordial dulness and the apex impulse is diminished. There is a diminution in the amount of urine and often a marked albuminuria. He is morose, sullen, and in a state of semistupor, gazing with dull, lacklustre eyes, scarcely conscious of his environment. The mental degeneration is complete and a continual delirium may be present. The condition of his heart and kidneys is such that restitution to a normal condition is impossible. Death occurs if the morphia is cut off, and the drug invariably kills if it is continued.

Considering the symptoms more in detail, memory is one of the faculties first affected and the amnesia is similar to the beginning senile dementia. Names are the first to go; the morphinist will relate occurrences early in his life, but will forget what he has done during the past week. He will forget the familiar names of streets, the details of his profession; thus the physician forgets the dosage of medicines and the scientific terms with which he is familiar. Others will make such errors in their daily work that they lose their positions. Amnesia of the well marked stage of morphia intoxication is only equalled by the amnesia of paresis. The will power is enfeebled and the patients spend days in bed without sleeping and without stupor; their minds are perfectly clear but their power to do is gone. They perceive the motive of actions and reason sanely, but all motive and reasoning is insufficient to produce effective volition. In some patients this is continuous and permanent; in others it seems to run in crises, lasting over two or three days. There is psychic asthenia. The sense of responsibility is wiped out and is replaced by the indifference of perfect egotism. Their character is modified and they are discontented grumblers, obstinately "ugly," often given to explosions of intense rage, quarrelling without cause, and even destructive and dangerous to those with whom they come in contact. They may become misanthropic, hypochondriacal, annoyed at trifles, and prone to seek solitude. Often the morphinists are individuals of more than average ability and intelligence, realizing fully their condition, and appreciating their progressive degeneration. It is for this reason that they resent criticism and accept reproaches about their habit with bad grace, because they are already filled with remorse. Morphinists will invariably lie about their vice, because in the early stages, they feel the disgrace and have enough moral sense left to endeavor to hide it. If, however, they have just taken their morphia or are assured of sufficient dosage to keep them comfortable, they do not necessarily lie about other matters. But when the craving for the drug is upon them, there is nothing to which they will not stoop to obtain it. Lying, thieving, begging in the street, prostitution itself, are to them all justifiable means to obtain the drug and smother the irresistible craving.

Contrary to what is often supposed, morphinists do not sleep well; they are subject to nocturnal hallucinations which render their nights times of dreaded fear and terror; thus they endeavor to keep themselves awake by reading, and during the daytime, when overcome by fatigue, are prone to fall asleep whenever they remain quiet, sitting in a chair, no matter in what place or company. These hallucinations

are extremely rare in the daytime. The hallucinations of sight are always terrifying, being composed of various animals, spectres, and of all sorts of revolting and gruesome combinations. Contrary to the hallucinations of alcoholism, those of morphinism are not occupation deliriums. The hallucinations of sight are much the most frequent; next those of hearing; those of taste and smell are rare, and those of general sensibility are exceptional, which last is also contrary to what occurs in alcoholism. The sense of taste itself is often dulled and sometimes even abolished. The sense of hearing is often noticeably diminished and the sight is affected, sometimes making walking difficult. Reading and writing become impossible because objects appear clouded and deformed, and when the endeavor is made to fix an object, it dances or trembles or approaches or retrogrades, and this, together with a frequent distinct photophobia, causes great distress. Ophthalmoscopic examination does not seem to reveal any distinct lesion. There is at times contraction, and at times dilatation, of the pupils; an anæmia of the retina has been described; sometimes the arteries seem scarcely visible with the venous congestion. These visual disturbances disappear when the morphia is permanently withdrawn. The reflexes are very variable. Disturbances of the general sensibility are often marked and vary greatly; there are often paræsthesias and sometimes intense neuralgic pains. Others show marked anæsthesia, which may be confined to one side of the body. More often there is hyperæsthesia, and the sole of the foot becomes so painful, that, when it is touched to the floor, it gives a sensation of burning, and the patient can only walk with short, jumping steps. Rodet considers this form of hyperæsthesia as very characteristic of chronic morphinism. The tactile sensibility is usually diminished or abolished. The question often arises whether indulgence in morphine impels the individual to suicide. At times when, inadvertently, too large a dose is taken, the patient succumbs, but as long as he can obtain his drug, he is an individual without will, apathetic, and incapable of making sufficient exertion to commit suicide; if, however, the morphine be withdrawn or he can not obtain it, the condition entirely changes and the symptoms and mental condition of morphia abstinence are, in many ways, the reverse of this.

Troubles of digestion are among those most noticed by the patients themselves; in the early stages there is nausea, vomiting, and anorexia, which do not persist for a very long time. There is often an intense thirst; the breath is very offensive and of a peculiar odor, often spoken of as being so characteristic as to designate the morphinist by those who are brought in contact with many of these patients. They are markedly constipated and this often alternates with attacks of diarrhœa; their stools are bloody and, during the period of constipation, may be as infrequent as once or twice a month. The teeth are subject to caries which attacks first the molars on their grinding surfaces; this extends to the bicuspid, then to the incisors, and last of all to the canines. This caries at times does not follow the above course but it is always painless, not accompanied by any periostitis, and usually progresses with great rapidity. Its occurrence usually coincides with the falling out of the hair. The disturbances of nutrition appear in some patients after a few months and in others not until after some years. Emaciation is perhaps the

the most striking and may go on to an extreme degree. Their faces become livid and often sallow, the expression set, and there are premature wrinkles, which, with the faded, sallow look of the skin, often gives the look of premature old age. The tissues lose their viability, which accounts in a measure for the ease with which slight bruises cause ecchymosis, and the greater liability to the occurrence of abscesses, to which we will refer later. Often in the skin there are multiple cicatrices and small spots from the use of the needle; as many as 63,000 have been counted on one individual.

The pulse of the chronic morphinist is slow and there is a fall in arterial tension with, in the last stages, distinct enfeeblement of the heart's action and diminution in the force of the apex beat. The number of respirations is slowed and, at times, they are shorter, so that every now and then a long deep inspiration seems necessary to give the required amount of air. Dyspnoea on exertion, even of the slightest kind, is quite common. In the beginning of morphia addiction, there is polyuria, which later is followed by a diminution of secretion below the normal. In many there is albuminuria which is ascribed by Levinstein to a special action of morphia on the medulla, to changes in the arterial pressure, or to a paralysis of the nerves which enter the kidney around the renal artery. The effects in the genito-urinary system are much the same as those described under opium.

Most women become sterile, but in spite of the cessation of menstruation, conception may take place. Pregnancy may run its normal course, or the morphia may cause a miscarriage or premature birth. Children born of morphinist mothers may be well-formed and normally healthy. Happel, of Tennessee, reports that in his experience a large percentage of children born of morphinist mothers have congenital cardiac defects. They showed, as so often seen in children of morphinist mothers, fretfulness, irritability, restlessness, and colic, which could only be relieved by opium. If they are not given opium, the restlessness and crying increase and they may go into a collapse in a few hours or live a few days and die from marasmus. If opium be given, they may be tided over for some months or years and perhaps a successful and gradual breaking off be accomplished. Often the children of morphia addicts are idiotic or show a lack of mental and physical development.

The accidents which may follow the injection of morphia are those of infection from the use of a dirty needle or of an infected solution. These abscesses usually appear at the point of injection, but sometimes at distant points, in a portion of the skin which has not been perforated. They are usually small, rather indolent, and not always as painful as one would expect. They usually heal under proper treatment, although they may form indolent ulcers. The points of injection may be the starting point of erysipelas, cellulitis, or phlegmon. Kane reports cases of tetanus developing from the hypodermic injection of morphia. In many morphinists the scars of the abscesses are very numerous on their legs and arms and even over the body. Where the morphia has been injected directly into a vein, sometimes a sudden, intense narcotism follows and the patient feels a peculiar tingling over the entire body. There is at times a feeling of great fulness and throbbing in the head and this may be accompanied by difficulty of respiration, swelling of the

face, and loss of consciousness. Death has been reported as following quickly when morphia is suddenly injected into the circulation. Most addicts increase the dose so gradually that the accident of acute poisoning and death from an overdose is comparatively rare. When, however, an endeavor has been made to reduce the amount taken and then for some reason a larger dose is desired, an amount, which formerly could be borne with impunity, is taken and death results.

When once a person is thoroughly under the influence of the habit, a cessation of the use of the drug produces symptoms, both physical and mental, of such intensity that few are strong enough to resist the craving thus produced and, unaided, break off the habit. When the effects of the last injection begin to wear off, restlessness, malaise, yawning, and sneezing appear; the craving increases and can only be entirely relieved by a further dose. The length of time, after the last dose, at which these symptoms will begin, depends on the individual. Following quickly on the malaise, the eyes begin to water and the eyelids droop. The eyes lose their lustre and vision is much disturbed. The face becomes pale and an expression of intense distress is very noticeable. Hearing is diminished and there is a mental hebetude which prevents all intellectual work. There is a trembling of the hands and of the arm in supination and pronation, varying markedly from the alcoholic tremor. In this condition there is nothing that morphinists will not do, and no means that they will not employ, in order to obtain morphia. As enforced abstinence continues, the patient may develop epileptiform attacks or hysteria, or there may be, in neurotic individuals, a state of choreic jactitation. In extreme cases a form of mania may develop in which the patients pace the room, shrieking, crying, throwing themselves about, using whatever instrument comes to hand to commit suicide, or they may attack their attendants. Hallucinations of sight and hearing may develop and these are always of a terrifying nature. This is most frequently seen in those who have taken alcohol with their morphia, but it not infrequently develops in those who have taken morphia alone. Often, before these mental disturbances are fully developed, the patients are overcome with a sensation of extreme weakness and forced to keep in bed. They are pale and haggard; there is nausea and vomiting, and almost invariably a diarrhoea develops, which may become extremely profuse. This is often accompanied with intense abdominal pain and hyperæsthesia of the skin so that the patient can scarcely support the weight of the bedclothes; the body is often covered with a cold sweat, and there may be chills of great intensity.

When morphia is cut off abruptly there is great danger of collapse. This may supervene on the second or third day and the patient shows increased weakness, appears pinched and haggard, while the pulse becomes small and then disappears. Or he may show a sudden high pulse tension, feebleness of the heart action, and suddenly, while wandering restlessly around the room, fall pulseless to the floor. Sometimes the fatal collapse may occur without warning while the patient is quietly talking or sitting in bed. Still another form of collapse may occur; the face becomes deep red, the eyes shine brilliantly, the pulse falls to forty and the patient loses consciousness after a feeling of intense agony. These collapses may last for fifteen or twenty minutes; they may recur three or four times in the

twenty-four hours, and the patient may recover or he may die in any of them unless morphia be given. Fortunately these attacks are rare when the drug is withdrawn gradually but they are fairly common when this is done abruptly. There are some few cases on record in which the fatal collapse occurred some time after the patient was convalescent and apparently had passed through the symptoms of abstinence and was well on the road to recovery. During their periods of suffering, the patients are apt to be afflicted with distressing insomnia and, if they sleep, it is only in fitful dozes. In a longer or shorter time the symptoms gradually disappear and the patient can rest with some degree of comfort; the morbid craving has gone; the appetite returns and often becomes excessive; in women menstruation is reëstablished, at first painfully, later normally. In both sexes the sexual desire returns, often painfully and excessively and then subsides. The patient goes into a rapid convalescence. When morphia is broken off, if it has been taken to quiet some neuralgia or to benumb some unbearable sensation, these pains, although quiescent during the period of the addiction, return in full force when the habit is broken.

Treatment.—The question often arises, whether the patient should be sent to some retreat, or whether a successful issue can be followed out at home. If the home treatment is decided upon, the family must be made to realize that they are dealing with the most cunning and cleverly deceptive kind of individual, who will stop at nothing, and who is probably concealing somewhere a supply of morphia. The suffering may be intense and will certainly be intentionally increased in order to obtain sympathy and to break off the treatment whenever it is possible. Too much stress cannot be laid upon the necessity of removing everything that can possibly be used for injury from the room in which the patient is to be. Even projecting hooks should be taken away, and the patient must never for a single instant of time, day or night, be left unwatched. In retreats or hospitals, the sufferings can be reduced to a minimum and when it is possible the treatment should always be carried on in some such institution. The question of the abrupt withdrawal or the slow method always comes into consideration. Levinstein, who used the abrupt method, says that he does not believe that this should be done unless the patient is otherwise healthy and suffering only from the symptoms due to morphia. This in itself shows the intensity of the strain and suffering that the abrupt method induces, and the danger of a collapse, which may be fatal, is most apt to occur in this method. The rapid method, by which the morphia is reduced to half the accustomed dose the first day and then half the next day and so in a few days is entirely withdrawn, is practicable in the majority of cases. The slow method, by which the drug is very gradually withdrawn, is useful for the very weak patients or those who suffer from some chronic disease and have gradually become addicted to excessive use. But in patients who are not afflicted with any chronic disease, it is apt to be extremely tedious and trying, really prolongs the suffering, and may discourage the patient, the physician, and the family.

The best method in the majority of cases, is to endeavor to find approximately how much morphia the patient has been accustomed to and cut it at least in half and give this amount in divided doses for the first twenty-four hours. It is very necessary to bring the digestive tract into as good a condition as possible, in the shortest space of time, which is best

done by the use of castor oil, in half ounce doses, three times a day, for the first week or ten days. When the patients are very weak, it is advisable to give subcutaneous injections of strychnine (gr. $\frac{1}{60}$ — $\frac{1}{30}$, gm. 0.001–0.002), at first every four hours. The best drug to equalize the circulation and to reduce the physical craving and suffering to a minimum, is the subcutaneous use of Livingston's solution of ergot as described under alcoholism. To allay the nervousness, warm baths are often very efficacious. Kane recommends that they be given at a temperature of 112° F., and the patient rubbed down quickly, placed in bed, and covered up warmly. To combat the insomnia, cold packs are often useful. A tonic of nux vomica and compound tincture of cinchona with capsicum, given three or four times a day, is of great assistance. Often in the first few days champagne or sherry is helpful, but this should not be prolonged, for these patients are as prone to take up other habits as they were originally to take to morphia. Chloral as a hypnotic has been condemned by most writers. Levinstein says that it tends to increase the excitement. Kane recommends bromides, given in large amounts of water, even in one hundred grain doses. The patient should be fed with koumyss and eggs as the most easily assimilated food. If accustomed to coffee and tea there is no reason why they should not be continued.

After the patients are over the worst of their symptoms and convalescence is established, they are by no means finished with their treatment. During the next six months the liability to relapse is very great and a single dose of opium or morphia will start them into their habit again. The cause for which they took the drug should be ascertained as accurately as possible and every endeavor made to change these conditions. They must fully realize that whatever mode of life brings the same temptations to them must be given up. Men may have to give up their profession and resort to some out-door existence and many professional men have succeeded in permanently curing themselves by going into the country and taking up some form of farming, stock-raising or flower-culture. The most difficult to cure are physicians or pharmacists, whose business leads them into the handling of morphia. It is said that about 80 per cent. of these relapse, and the relapse is more difficult to treat. Even after years of freedom the danger has not ceased and the writer knows a patient, who after eleven years of abstinence, fell into the habit again because, during an attack of pleurisy, he was given morphia by a physician and this against his protest. A certain number can be cured and, although the percentage of relapses and failures is very great, each individual should be treated on the supposition, however apparently hopeless, that he may be the one in whom success is possible.

COCAINE.

At the time of the Spanish conquest of South America, the Indians of Bolivia, Peru, and Colombia, were found to be using the leaves of *Erythroxylon Coca* to sustain their strength during fatiguing journeys and to alleviate the sense of hunger and thirst. Coca was used in the religious rites of the Incas and was treated by them with great reverence, being employed in their sacrifices to the Sun, the high priest chew-

ing the leaf during the ceremony. Before the arrival of the Spaniards it was sometimes used as a medium of exchange. Nicholas Monardes, a Spanish physician, published, at Seville, in 1565, a history of medical simples brought from the new world. He describes the use of coca among the South American Indians as being of three kinds; it was chewed and mixed with the powder of calcined shells of oysters and other shell fish; this paste, after being allowed to ferment, was formed into boluses or troches and allowed to dry; during long journeys these were sucked and, under their influence, hunger and thirst were alleviated and fatiguing journeys sustained; when eaten for producing pleasure or intoxication, the coca was chewed by itself; and third, it was mixed with tobacco and smoked. The Spaniards, not understanding the action of coca, regarded it with superstition and the Council of Bishops at Lima, in 1569, condemned its use on the ground that the belief entertained by the Indians, that chewing the coca gave them strength, was a delusion of the devil. During the last century many observers noted the extraordinary endurance of the Indians under its influence, but it was not until Koller, in 1884, discovered the local anæsthetic properties of cocaine when applied to the eye, that its use became generalized as a medicinal agent. At first it was considered harmless, but before long it was evident that continued use brought with it a seductive addiction, which was broken up with difficulty and produced very rapid and destructive effects.

The pure cocaine addict is not as commonly met with as the morphinist or the alcoholic. The drug is usually taken to overcome the nervousness of an alcoholic debauch or the depression following morphine. It is not infrequently used to relieve the exhaustion following sexual and alcoholic excesses. Judging from the statistics of drug store sales, cocaine addicts seem to be most common among the very poor and among the wealthy. Cocaine is contained in certain quack nostrums which are sold extensively in certain sections of the country by itinerant peddlers. In the Southern states, cocaine addiction is very common among the negroes, who speak of it as "tabs" because it is bought by them in tablet form. Snuffing the powder or a solution of cocaine is a common method of use. It is often taken hypodermically, and, when thus used in impure form, it sometimes causes a green discoloration, which remains permanent at the site of the injection in the skin. One woman who came under the care of the writer had, on her hips, thighs, and legs, so many of these little, round, green spots, about a centimeter in diameter, that there was scarcely a square inch from her waist to her knees which did not contain one of them. Patients suffering from neuralgia, local or general, physicians exhausted and anæmic, who have to be tided over some strain, neurotic and psychopathic individuals, the worn-out and failures of modern life, fall easy victims to the pleasing and soothing effects of this drug.

Acute cocaine poisoning is seen following the injection of the drug to obtain its local anæsthetic effect in surgery. Death is reported as having occurred in forty seconds following twelve drops of a 4 per cent. solution given hypodermically to a girl of eleven years. Half a grain to one unaccustomed to its use seems often to be a border-line dose. Such small doses as four drops of a 2 per cent. solution in

the eye, produced in an old woman an intoxication which lasted for four days, and eight drops of a 10 per cent. solution in the eye of a girl of twelve produced violent symptoms of poisoning, and even one drop of a 1 per cent. solution in the eye of a child fourteen years old has been followed by symptoms of active poisoning. It is evident that there is a strong, personal idiosyncrasy, and while such small doses have caused death, recovery has followed such large doses as twenty-two grains by the mouth, and ten grains hypodermically. In the mild cases of poisoning the ordinary symptoms are great restlessness and nervous excitement, with no feelings of pleasure or comfort, but rather those of anxiety and even terror, an increase in the frequency of the respirations, and often a distinctly accelerated pulse rate, with the patient pale, faint, and dizzy. In the more severe poisoning there has been nausea and vomiting, a rapid and imperceptible pulse, great nervousness and jactitation; the patient feels as if the heart would stop beating; intense perspiration and collapse with or without loss of consciousness is seen; the pupils are usually dilated; in some they have been reported as contracted, and, occasionally, the pulse has been slow and feeble with slow and infrequent respiration, or Cheyne-Stokes breathing with marked cyanosis. After large doses, convulsions are frequently present and are often of a violent epileptiform character. At times these are partial, with unilateral or bilateral cramps in the muscles, chiefly in the flexors; these muscular spasms may go on to general rigidity and opisthotonos may be produced. Consciousness is usually lost but sometimes there is mania with hallucinations and delusions which have frequently been violent and even homicidal. The treatment of the poisoning is symptomatic; the patient should be kept in a horizontal position and given aromatic spirits of ammonia, alcohol, camphor, or caffeine. If the poisonous effects are manifested in the respiration, oxygen or even artificial respiration should be used. Intravenous injections of normal saline solution have proved helpful. If the drug has been taken by the mouth, the stomach should be washed out. After the patients have recovered from this acute poisoning, nervous disturbances, such as insomnia, vertigo, tingling in the limbs, and mental depression, may continue for some days.

Chronic poisoning by cocaine is both periodic and continuous. The periodic form is characterized by the excessive use of the drug for several days or weeks, after which it is abandoned and there is a period during which there is no desire for it. During the free intervals the patient remembers distinctly the pleasurable mental impression which he obtained, declares that he has broken from its use and that he will not use it again, but as soon as the cause returns which formerly drove him to the use of the drug, he will invariably reason that there is no danger in using it for a short time, and quickly returns to its use. Soon the free periods become shorter, and those of addiction longer, and its use becomes continuous. Few indeed of the cocaine addicts remain periodic takers. These persons also show the peculiarity which is especially marked in the addictee of cocaine, that in order to conceal its use, they will take other drugs such as alcohol, chloral, and morphine, and when they cannot obtain cocaine they will turn to any drug that will quiet the nervous system. Some patients become violently mania-

cal, requiring several persons to restrain them and, when given the drug, almost instantly quiet down, with all symptoms of their mania gone.

The main pleasurable action of the drug is the feeling of exhilaration and increased mental and muscular strength and with this there soon develop delusions of great strength and vigor, the patient feeling as if he had absolute self-possession; he shows great activity, talks freely and enjoys everything; each sense seems to be greatly heightened; there is an increased pleasure in taste, and the keenness of smell is heightened. Finally hallucinations of voices begin to appear; there are delusions of persecution and fears of personal injury; insomnia comes on with great muscular restlessness and agitation, which simulates the irregular spasmodic movements of chorea major. They show a profuse volubility, talking in a wide discursive manner over all subjects and in their writing or speech there are no pauses, no dividing lines, no purposeful connection but a steady, connected flow of words, involved and without point, without direction, and without end. The patient will endeavor to convey some idea or belief, and after the first few sentences the purpose is forgotten and he wanders on in great prolixity and diffuseness. Thus many cocaineists are great letter-writers, and in some instances the letters have taken on an amatory type. This same prolix type, in other instances, has taken on a slanderous form, but there is a noticeable lack of bitter, sharp accusations and distinct charges; the meaning of the letters can only be made out by inference from the involved mass of words. Again, hallucinations of sight and hearing develop, and the patients see suspicious characters watching them and hear voices plotting to do them injury; they begin to take unusual precautions and are prone to carry revolvers and knives to defend themselves, and justify such procedure by the explanation that their lives have been, or are, in danger.

In the early stages of cocaineism, when the effect of the drug begins to wear off, the patients become morose, irritable, easily excited, and suspicious; there is insomnia and an impending sense of trouble and danger. In the later stages, the exaltation periods are brief and are followed by stupor and restlessness with evidences of great mental disturbance. The appetite fails; they are anæmic, and emaciate very rapidly; look sleepy and tired; the skin becomes flaccid and pale; the senses of sight, hearing, and smell, are seriously impaired, and there is a feeling of paræsthesia in the skin, giving a sensation as if vermin were crawling on it, which is a very significant symptom. Although there is increased sexual excitement, the sexual power is diminished. Kraepelin describes a definite psychosis which may develop on the basis of chronic cocaineism and which bears a close resemblance to alcoholic delusional insanity. It begins with a few days of irritability, anxiety, and restlessness, after which the hallucinations suddenly appear. Threatening voices are heard compelling the patients to act strangely; moving pictures are seen on the wall, filled with large and small objects. Minute black specks, moving on a light surface, are very characteristic hallucinations, and may be mistaken for flies, mosquitoes, and other small objects. Paræsthesias of the skin create the belief that they are under the influence of electricity, are being punctured with needles, or are poisoned. Most characteristic is the sensation of foreign bodies

under the skin, particularly of the ends of the fingers and palms of the hands. The muscular twitchings are thought to be due to poison. Auditory hallucinations make them suspicious of their surroundings. They believe their thoughts are secretly being read or they are being spied upon through holes in the ceiling. The patients may try to kill their alleged tormentors or attempt suicide. They have characteristic delusions of infidelity which come on as an acute symptom. These are often obscene in character and they will accuse their wives of the grossest immorality. They are prone to react to these false ideas in a vindictive and aggressive manner. Consciousness remains clear and orientation is good except in rare instances when the excitement is very great or after the fresh injection of the drug. The emotional attitude of these patients is dejected, excitable, irritable, and even passionate; more rarely they are reserved and reticent concerning their delusions. Their actions are usually restless and unstable though some may appear orderly.

Cocaine delusional insanity develops rapidly and may run its full course in a few weeks. The symptoms increase under the influence of a single dose. The delirious state soon disappears if the drug be completely withdrawn, but the delusions may remain for weeks or months. Morphinism and cocainism in the same individual often lead to a combination of symptoms, but morphinism, except with cocainism, seldom produces a rapid development of pronounced mental disturbance. The cocaine psychosis develops more rapidly, the symptoms are more severe than in the alcoholic delusional insanity, and the delusions of jealousy appear earlier and are an acute symptom. A single dose of cocaine produces an exacerbation of the symptoms, while in alcoholism it produces little or no effect. The sensation of objects under the skin is characteristic only of cocainism.

Diagnosis.—The diagnosis of cocaine addiction is often very difficult. In some patients there is only an increased buoyancy of spirits and an increased desire for mental and physical exertion, but if their work be studied closely it will be seen that its character, and the judgment displayed in doing it, are below the former excellence. These patients show defects of judgment and a diminished sense of ethical duties; they are also more prone to be reckless and aimless in their thoughts and work, and show a diminution of ambition and will-power. The powers of connected application are less, and often a noticeable symptom is periods of buoyancy varying with periods of beginning depression, and a disposition on the part of the patient to go off alone; and on his return the old buoyancy and confidence have returned. Thus the cocainist differs from the alcoholic, by his periods of secretive solitude, and from the morphinist, in the later stages, by his delusions of persecution. When cocaine is the main drug and alcohol and morphia are taken to relieve it, the periods of exaltation and delusions of persecution are very noticeable. If, however, cocaine is taken to relieve morphia or alcohol, the peculiar symptoms of cocaine are usually absent and there is simply a restlessness and insomnia. Morphine and alcohol, taken after cocaine, intensify the injury to the nervous system and both mania and dementia are apt to follow. Thus the combination of these drugs renders the prognosis graver and the danger to relapse greater.

Prognosis.—As regards the prognosis in the early stages, where cocaine is taken alone, if the proper treatment can be instituted, the habit seems to be more easily broken than that of morphia or alcohol and the chances of a permanent cure and restoration to health are also greater. If, however, the habit is well-established, the prognosis is unfavorable for complete recovery. The drug causes its destructive action more quickly and more intensely than alcohol or opium.

Treatment.—In treating cocainism we must realize that there is no drug which brings with it such a blissful sense of satisfaction and of relief from mental or physical pain, or gives such a sense of increased vigor and the ability to do all that the mind craves or hopes for. The effect thus produced is very intense and, although the patient may realize the danger of relapsing, the mental impression made under the influence of the drug is so strong that the tendency to relapse is very great. The amount taken by the cocainist varies and has been given as from thirty to forty grains a day by mouth or hypodermically; it also varies widely with the individual. The greatest amount which has come under my personal observation was in a young woman who took twelve grains of morphia and sixty grains of cocaine a day, by the hypodermic method. The withdrawal of the drug should begin at once; sometimes this can be complete; at other times tapering-off must be allowed, especially in the patients in whom the symptoms of maniacal excitement follow its withdrawal. If morphinism and cocainism co-exist, cocaine should be withdrawn first. Substitutes should be used to lessen the irritability and the distressing symptoms caused by withdrawal. The best of these seem to be valerian, hyoscyamus, and vegetable narcotics of this type. Bromides are often useful in large doses for a short period. If there are symptoms of collapse, camphor, caffeine, or strychnine, must be used. Chloral, alcohol, and opium are unsafe. The conditions are usually those of starvation and cell poisoning and, therefore, the digestion should be carefully watched, and often, in the beginning, continued doses of castor oil, such as a half ounce or an ounce three times a day, are necessary. The insomnia should be treated largely by food and prolonged warm baths. These patients should be sent to some asylum or retreat to be cared for until the acute symptoms have subsided. After a shorter or longer time, they may be sent back to the care of the family physician, but a long period is required with constant care and surveillance, and absolute change of surroundings and conditions of life. These patients are especially prone to refuse co-operation with the physician and, from fear or pride, conceal their real condition. The closest study of the causes and conditions which brought about their addiction must be made and it is only by the removal of these causes, and their prevention, that the patient will ever be broken of this habit.

CHAPTER XI.

FOOD POISONS.

By FREDERICK G. NOVY, M.D.

WHENEVER a given article of food becomes a vehicle for an injurious agent it is for the time being, a poison. Such a food *acquires* its poisonous property, in distinction from that which is *always* injurious. In the latter instance we are dealing with plants or animals in which the elaboration of poisonous substances is a normal physiological process, as in certain mushrooms and fish. The poison of such may be said to be of endogenous origin, whereas in the former it is accidentally present, from an outside source, and is therefore exogenous.

Poisonous metals, animal parasites, and bacteria, make up the three chief causes of unwholesome food. Accidental poisoning from metals in the food is the least common occurrence, so much so, that in nearly all ordinary intoxications the question of the presence of metals may be disregarded. Nevertheless, notable outbreaks of this nature have been known even in recent years. Thus, the famous "beer epidemic" of Manchester and other English cities, in 1900, was due to the accidental presence of arsenic. Other poisonings, caused by water which had taken up lead or zinc, are so well known as scarcely to need mention. The wide use of canned goods suggests the possibility of these becoming poisonous by the solution of tin or solder, but the small amounts of these in solution could only manifest an action after the prolonged and exclusive use of such foods, a condition which never obtains in ordinary life.

The animal parasites, such as trichina and cysticercus, are also of relatively little importance, especially in comparison with the group of bacteria. The latter constitute the chief factor in poisonous foods. At times, food may be derived from diseased animals, and injurious effects may be directly due to the presence of the specific germ, and the poisoning represents actually an infection. At other times, food may become accidentally contaminated with germs, such as typhoid bacilli, and may give rise to veritable epidemics. And lastly, food may be invaded by bacteria which are themselves unable to grow in the living body but form their poisonous products directly in the food. The more detailed consideration of these causes will be given in connection with each kind of food.

POISONOUS FISH.

The ill effects following the use of fish (Ichthyismus or Ichthyotoxismus) may be due to a number of causes, some of which are well understood while others are still far from being satisfactorily explained. Obviously,

poisonings of this kind are relatively more frequent in countries in which fish form a large part of the diet, notably Russia, Japan, and the West Indies. The several causes may be grouped in the order of their importance under four heads. First, the presence of normal or physiological poisons in the fish; second, the presence of bacteria or their products; third, invasion by animal parasites; and fourth, contamination with metallic or other poisons.

1. Physiological Poisons.—It is well recognized that there are many fish which are always poisonous, while others may become so during the spawning season. The consumption of such fish may lead to severe and even fatal intoxication. Thus, in Tokio alone, from 1885 to 1892, there were reported 993 cases of so-called fugu poisoning, of which 680 were fatal—a mortality of more than 68 per cent. At times even, notably in China and Japan, such fish are taken for suicidal purposes. The fugu poisoning of Japan and the East Indian Islands is due to various species of *Tetrodon* and *Diodon*. The active agent, which resembles curara somewhat in its effects, is present in the ovaries and testicles. The earlier Japanese investigators designated this substance as *fugin*. The exact nature of the poison is not determined. The symptoms of fugu poisoning resemble those of curara. There is dyspnoea, cyanosis, dilatation of the pupils, relaxation of the sphincters, paralysis of speech, dizziness, salivation, and vomiting. After the onset of the symptoms death may result in from one to two hours.

While the organs of the several species of *tetrodon* are always poisonous, there are other fish which become toxic only during the spawning season. Under these conditions the roe of different members of the sturgeon family, of the pike, and the barbel, have been known to cause pronounced and even fatal intoxications. The symptoms are those of an acute gastro-enteritis.

As further illustrations of physiologically poisonous fish may be mentioned the cod-fish (*Gadus morrhua*), *Perea venenosa*, and *Sparus Mæna* which, eaten in the raw condition, have been known to cause grave intoxications.

2. Bacterial Poisons.—As might be expected, intoxications arising from this cause are fairly common and may be met with under various conditions. Thus, the fish may be diseased and the infection be transmitted when the flesh is eaten raw. The fish when caught may be perfectly wholesome but, as a result of imperfect preservation, bacterial contamination may occur with the production of poisonous products. It is necessary, therefore, to consider these two types of infection separately, especially since a similar condition will be noted in connection with other foods.

Epidemics among fish have been repeatedly observed in this and other countries, but it is only within recent years that they have been studied from the etiologic standpoint. It is not within the scope of this article to consider such outbreaks except in so far as they throw light upon the subject of poisonous fish. That the consumption of such diseased fish may cause intoxications, and even actual infections, may be theoretically conceded even if such occurrences are few in number.

Fischel and Enoch, in 1892, isolated from a carp, which died during a fish epidemic, a spore-bearing bacillus (*B. piscicidus*) which was patho-

genic for mice and guinea-pigs. The toxin elaborated by this bacillus was readily destroyed by boiling. From diseased trout, Bataillon, in 1894, isolated a bacillus closely related to *Proteus vulgaris*. It was apparently pathogenic for pike, crabs, and frogs. In the same year Emmerich and Weibel studied another epidemic among trout in which they found a bacillus (*B. salmonicida*) differing from the preceding. Similar observations were made in 1893 by Charrin in connection with a barbel epidemic in the Rhone, and by Canestrini, who isolated from diseased eels a bacillus resembling that of cholera. This was pathogenic for fish and frogs, but not for mammals.

One of the most interesting studies of fish infection is that of Sieber-Schoumow. Two outbreaks occurred among the fish in a palace reservoir at St. Petersburg, in 1894, and on both occasions she isolated an organism which she named *B. piscicidus agilis*. This germ was found not only in the diseased fish but also in the water and on the bottom and walls of the reservoir. The bacillus was also found in a large number of the fish on the market at the time, and also in the discharges of two cholera patients. An attempt at isolating the active poison failed, although the presence of cadaverin and other ptomaines was demonstrated.

During an epidemic in Lake Zurich, in 1898, Wyss isolated a liquefying bacillus which he considered to be identical with Sieber-Schoumow's bacillus and *Proteus vulgaris*. The organism was pathogenic for fish, mice, and guinea-pigs.

The outbreaks mentioned above were not associated with any instances of poisoning in man, though it is reasonable to believe that, if the fish had been eaten in a raw or partially cooked condition, such results might have followed.

In the first place, the pathogenic organism in the fish, as is readily conceivable, may cause a real infection in man. And again, it will be presently shown that poisonous fish may contain a soluble toxin which is readily destroyed by heat, and consequently, fish carrying such bacterial products would be dangerous only when consumed in the more or less raw condition. In this and in the preceding case an essential factor is that the food be eaten in a raw state, since cooking destroys bacteria and certain toxins. On the other hand, it is possible to have toxins which resist boiling, and consequently food infected with bacteria which produce toxins of this type might prove injurious even after thorough cooking. Thus, Sieber-Schoumow found that macerations made from infected fish, after boiling for half an hour, were still capable of causing fatal intoxication. This and similar observations indicate the necessity of distinguishing between these three types of bacterial action.

The observations of Arustamow, made in 1891, are usually taken to indicate the effects of diseased fish. He studied eleven cases of fish poisoning of which five ended fatally. These were caused by the consumption of four kinds of fish which were eaten in a raw, salted condition. The fish, though somewhat soft, were of good appearance and showed no sign of decomposition. The process of salting, however, was not very effectual, since the entire bodies were found to be permeated with living bacteria. From the fish and the organs of the fatal cases he isolated four kinds of bacteria, of which two, however, were particularly studied. Dur-

ing the past year these two organisms have been studied by Konstansoff, who arrived at the conclusion that the bacillus obtained from the salmon was an ordinary *Proteus vulgaris*, while that isolated from the sturgeon was a variety of the *B. coli*.

The studies of Konstansoff¹ are particularly valuable, inasmuch as they throw new light upon the nature and origin of the fish poison. His material was a sturgeon which poisoned two people. The fish was of good appearance and showed nothing abnormal. All attempts at demonstrating the presence of bacteria, either in stained preparations or by the usual cultivation methods, failed; in other words, the material was sterile. This was due to the fact that the sturgeon was well salted, containing as much as 15.6 per cent. of sodium chloride. Experiments made with ten different organisms showed that when these were planted in broth containing 15 per cent. of salt, no growth took place, and, moreover, all died out (spores excepted) in from three to five days. When fish were injected with such cultures and then salted they were found to be practically free from organisms after the twentieth day. In view of the fact that fish are not salted immediately after being caught but are kept for some time and even transported to a considerable distance, it is evident that partial decomposition may set in, especially if the fish were infected or diseased when taken. The subsequent salting inhibits the further growth of such organisms and even destroys them, but the poison which they have already formed persists and can only be removed by boiling.

An emulsion of the sturgeon was found to be highly toxic to small animals, especially when administered by injection. In rabbits the intoxication lasted for several days and was marked by nervous phenomena, such as clonic contractions of the extremities. At autopsy the most noticeable feature was the rose color of the tissues and blood, a condition which has been observed in man after fish poisoning and is suggestive of the action of hydrocyanic acid. A suspension of the fish after passage through a filter paper and then through a Chamberland filter gave a filtrate which was as toxic as the original liquid, but the solid residue after washing was found to be wholly inert. Attempts at extracting the poison by means of alcohol or ether failed. The above filtrate was rendered inert by boiling, and even an exposure of half an hour at 50° C. was sufficient to destroy its toxicity. This behavior to solvents and to heat clearly shows that the soluble poison is not of the nature of a ptomain but rather is a toxalbumin or more correctly a toxin, and, as such, approaches those of diphtheria and tetanus. Like the toxin of tetanus, the fish poison tends to accumulate in certain organs and tissues. Thus, in a poisoned rabbit the toxin was found localized especially in the muscles and to less extent in the nervous tissue and in the liver.

From Konstansoff's investigations of the conditions under which normal fish give rise to this or a similar toxin, it is certain that bacteria are necessary. In ordinary putrid decomposition of fish various poisonous products are formed, some of which resemble the above toxin while others are of the nature of ptomains. It is generally recognized, since the work of Brieger, that highly poisonous products are to be found only

¹*Archives d. sciences biolog.*, 1904, 10, p. 475.

during the first days of putrefaction and that they disappear as this progresses, giving rise to relatively non-poisonous ptomaines. In other words, the products of the initial changes, which are hardly recognizable by the sense of smell or taste, are more dangerous than those of advanced decomposition. Konstansoff showed that a uniform distribution of bacteria in the fish, a condition which is best realized when the fish is diseased or septicæmic, insures a uniform production of toxin in the tissues. The salting of the fish at this stage arrests all further decomposition, but the toxin already elaborated remains unchanged and, as a result, such fish, when eaten raw, cause the well-known symptoms of intoxication.

The symptoms observed in this type of poisoning, as well as the properties of the toxin *in vitro*, resemble very closely those of *B. botulinus*, which, as will be shown, produces the most severe type of meat poisoning. The presence of this organism in fish has never been established, and until this is done it will be best to regard these two kinds of intoxication as etiologically distinct. The ill effects after eating such raw fish appear in from ten to twenty-eight hours. The fatal result, when it supervenes, occurs only after several days, and at no time has it been observed within the first twenty-four hours. The quantity eaten has no necessary relation to the severity of the symptoms. Thus, a small amount may prove fatal, whereas a larger portion may be followed by recovery. This peculiarity is probably not due to idiosyncrasy or to an uneven distribution of the poison in the fish but depends rather upon the quantity of food in the stomach. The dilution caused by the presence of a large amount of other food, and the consequent retarded absorption, may favor the destruction of the poison by the digestive fluids.

Symptoms.—The symptoms are general weakness, dull pain in the abdomen, dyspnœa, mydriasis, impaired vision, diplopia and vertigo, complete dryness of the mouth and tongue, inability to swallow, and loss of speech. Vomiting and diarrhœa are absent and instead there is obstinate constipation and retention of urine. Vomiting is absent at first but may come on in the later stages. There is no rise in temperature and, on the contrary, there may be a fall of several degrees, especially before death. Another type of bacterial poisoning from fish presents an entirely different train of symptoms. It is of the nature of an acute gastritis and gastro-enteritis. Violent vomiting, excessive diarrhœa, dizziness, tremor, prostration, and cardiac syncope are observed. Autopsy shows extensive follicular enteritis with necrosis, hyperæmia of many organs, fatty degeneration of the liver, and toxic degeneration of the heart. These symptoms and changes were observed in recent fish poisoning at Zurich in which fourteen persons were affected, two of whom died within twelve hours. From the fish and from the spleen and blood of the deceased persons, an organism was isolated which was identified with *B. enteritidis*, which is an important cause of meat poisoning. This outbreak therefore, unlike the above, is clearly an infection and intoxication.

In view of the fact that poisonous products are met with in the raw and imperfectly salted fish it is evident that like substances may develop in canned fish. Indeed, serious results have followed the use of canned salmon, as is reported by Ballard. In spite of the fact that the can was "blown" and the contents partially decomposed, they were consumed by

five persons. Three of these recovered, while one who ate the most became ill about ten hours after eating, and died in three days. Another who ate somewhat less died in five days. No organism could be obtained from the fatal cases, or from mice which died after being fed some of the salmon. This would indicate, as in Konstanoff's experiments, the presence of a soluble toxin.

From some canned salmon which caused poisoning in a man, Vaughan isolated a micrococcus which was found to be highly toxic, especially when grown under anaërobic conditions. About twelve hours after eating this fish the patient began to suffer from nausea, vomiting, and a griping pain in the abdomen; and six hours later he was found vomiting small quantities of mucus, colored with bile, at frequent intervals. The pulse was 140, the temperature 102° F., and the respiration shallow and irregular. A scarlatinous rash covered the entire body but disappeared in the course of the next day; the temperature remained above the normal for four or five days, and eventually complete recovery followed.

Summing up the observations which have been made thus far upon the rôle of bacteria in fish poisoning, it is evident that many bacteria, especially of the Colon and Proteus group, take part in the process. These may be present in diseased fish, or they may be introduced after the fish are caught. In either case, during the initial decomposition changes which are scarcely recognizable, there are formed poisonous products, which in some instances are readily destroyed by heat while in others they are not affected. The ingestion of such fish is followed by a more or less severe intoxication, depending largely upon the kind of organism present, and at times by actual infection.

Animal Parasites.—Under this head it is sufficient to mention the numerous infections with *Bothriocephalus latus*, directly traceable to the eating of fish infested with the larvæ.

Metallic and Other Poisons.—Poisoning from canned fish is sometimes ascribed to the presence of tin and other metallic poisons which have been dissolved out by the acid or ammoniacal contents. It is known that appreciable amounts of tin can be obtained at times from canned goods, but that fact in itself is insufficient to explain the effects observed. In all such cases, decomposition of the contents by bacteria offers a more rational explanation.

Some cases of poisoning have been ascribed to the food taken by the fish, such as poisonous medusæ and corals, and decomposing proteids. Without doubt, fish may become infected by eating putrid food or by living in contaminated waters, but when this does occur the resulting poisoning properly belongs under the head of bacterial poisons. The symptoms which have been noted in such cases, are either those of an acute gastro-enteritis or are of a nervous order, and correspond to those already given.

POISONOUS SHELL-FISH.

The conditions which render such food poisonous are much the same as those which have been given in connection with poisonous fish. Thus, there is always the possibility that the molluscs may be diseased at the time they are gathered, in which case the infection is transferred to the

consumer. The existence of such disease, however, has not been established as clearly as in the case of fish. A second condition is to be found when such food is perfectly wholesome at first, but on keeping, as a result of even slight decomposition, becomes toxic. With this, as with other foods, the initial products of putrefaction are the most dangerous. For example, mussels which have been allowed to decompose for some days have been shown to be free from poisonous substances. It would appear that the first products of the cleavage of proteids and of lecithins are especially poisonous, and that by the further action of bacteria these are then converted into less toxic, or even inert, bodies.

The most important condition which bears upon the toxicity of molluscs is their habitat. It has been repeatedly demonstrated that when these are grown or kept in polluted waters, they acquire toxic and even infectious properties. On being transferred to fresh clean water, they soon lose their poisonous character. The fact that perfectly fresh mussels at times cause severe and even fatal intoxications, would seem to indicate that the elaboration of the poison may occur during the life of the animal. It is because of this that some writers consider such products to arise by tissue metabolism, and hence designate them as "leukomains." Others have expressed a belief in the existence of a distinct poisonous variety of mussel, while still others have held that the mussels had taken up poisonous food material or even metallic poisons. Such views are, however, no longer considered seriously, since the condition mentioned can be accounted for more easily by the known facts regarding the presence and action of bacteria. Molluscs living in polluted waters are known to take up large numbers of different kinds of bacteria which they may maintain in a viable state for a considerable length of time. Without doubt some of these organisms are able to act upon the host, and thus give rise to poisons, but the exact conditions under which these products are formed in the living mussel are as yet undetermined.

Of far more importance than the occasional poisoning from shell-fish is the fact that these convey specific infections to man. It has been established beyond a doubt that oysters and other molluscs are a prolific source of infection. A marked instance is that afforded by the mayoralty banquets which were held at Southampton and Winchester, in 1903. Of the 132 guests at the former 55 became ill, and all but one of these had eaten oysters; 11 developed typhoid fever. Of 134 guests at the latter place 62 became ill and 10 of these had typhoid fever. The evidence showed that the oysters had been gathered at the same place, from beds which were polluted with sewage. An examination made by Klein showed the presence of a germ belonging to the *B. enteritidis* group.

The studies of Herdman and Boyce have served to call attention to the extreme contamination which may occur. Thus, from the cavities of oysters obtained from the neighborhood of a drain-pipe they obtained as many as 17,000 colonies, against 10 colonies which were present in oysters secured in open water. On placing oysters in water infected with typhoid bacilli it was found that these organisms were ingested and that they could be isolated from the cavities in some cases as long as fourteen days after the infection. Klein has found the typhoid bacilli to persist in oysters for from two to three weeks. At times, however, the

oysters may clean themselves within a week. This is facilitated to a marked degree by placing them in clean water which is constantly being renewed. The disappearance of typhoid and colon bacilli from infected oysters, while in part the result of elimination, is probably largely due to destruction within the body of the mollusc. It is evident that, under favorable conditions, self purification of the oysters may be secured.

In view of the above facts it is reasonable to believe that other infections, such as cholera and amœbiasis, may in some localities be spread through the agency of contaminated molluscs. Positive evidence on this point is as yet wanting.

Mussels.—Poisoning from the common mussel (*Mytilus edulis*) is by no means a rare occurrence in England and on the Continent. The symptoms of intoxication are subject to considerable variation. In general three types are to be recognized. The first partakes of the character of a gastro-enteritis. The choleraic symptoms, such as nausea, vomiting, diarrhœa, do not appear until after the lapse of some hours. Death may result, but not as a rule. This type corresponds to similar forms of intoxication caused by meat, cheese, and other foods.

A second type of intoxication presents essentially nervous symptoms, and is the most common form. It begins with a sensation of heat. Itching appears, usually at first in the eyelids, but before long spreads over the face and may involve a large part of the body. A diffuse exudative erythema, or general urticaria, develops. Angina and dyspnœa are at times pronounced. In this form, recovery usually takes place after a few days.

The third type is paralytic and suggests the action of a curara-like body. It is less frequent and more dangerous than the preceding forms. To a certain extent it may be compared with the intoxication caused by Konstansoff's fish toxin, or with that of Van Ermengem's *B. botulinus*. It differs from these, however, in the rapidity of the onset of the symptoms and in the fact that boiling does not destroy the poison. The apparently perfectly fresh mussel may cause a rapidly fatal intoxication, as has been noted in England in several instances. Thus, in one case, the symptoms came on almost immediately after eating boiled mussels and death occurred in fifteen minutes. In another case the mussels were gathered from water known to be polluted, and, although they were washed and cooked thoroughly, in several changes of water, yet they poisoned two persons, one of whom died. Four hours after eating the meal they were seized with giddiness and were unable to stand or sit up. They showed mental excitement or delirium, closely simulating early alcoholism. There was numbness of the extremities, diminished sensation, and dilated pupils. The abdomen was distended and tympanitic; constipation was present. Dryness of the throat, constriction in the neck, difficulty in breathing and swallowing, and a tendency to syncope were prominent symptoms. The temperature was normal, and the pulse did not go over 80. One recovered in two days.

One of the most conspicuous examples of mussel poisoning was at Wilhemshaven, in 1885, where a large number of dock laborers and their families were affected. According to Schmidtman the symptoms developed shortly after the cooked mussels were eaten, or within a few hours, according to the amount consumed. They began with a feeling

of constriction in the neck, mouth, and lips. The teeth were set on edge as if sour apples had been eaten. There was a pricking, burning sensation of the hands, and later of the feet. Giddiness followed but no headache; a feeling of lightness of the body, with a sensation of flying and general excitation similar to that of alcoholism, restlessness, some anxiety, with slight distress in the chest, were present. The pulse was hard and rapid (80-90) without any increase in temperature. The pupils became dilated and reactionless but there was no impaired vision. Speech became difficult, broken, and jerky, and the limbs heavy and stiff. The patients became dizzy, staggered and grasped spasmodically at objects which they missed, and finally the legs were no longer able to support the body. Then came marked nausea and vomiting but no abdominal pain or diarrhœa; there was numbness of the hands and coldness of feet at first, gradually extending over the whole body, with a feeling of suffocation; in some cases abundant perspiration, followed by quiet, restful sleep. Death occurred in one case in one and three-quarter hours; in a second, in three and one-half hours; and in a third, in five hours, after eating the mussels.

The chemical examination of the poisonous mussels was made by Brieger, who succeeded in isolating several bases or ptomaines, one of which (*mytilotoxin*) proved to be highly poisonous. The effect produced by this in animals was the same as that which followed the administration of boiled extracts of the mussels. Therefore, intoxications of this type are due to a heat-resisting alkaloid, or ptomain, and in a sense are analogous to those caused by poisonous mushrooms. The production of the poison, however, is not a physiological one, as in the latter, but the result of the action of bacteria in the polluted water.

Oysters.—The part played by oysters in the spread of typhoid fever and other infections has already been given, and there remains to be considered the acute intoxication to which they at times give rise. Gastro-intestinal disturbances of variable intensity have been repeatedly met with, and have been shown to be due to oysters derived from sewage-polluted beds. The intense poisoning, such as is given above under mussels, is fortunately not a common occurrence. A striking instance is reported by Brosch, in 1896, in which an officer died in twelve hours after eating some oysters which at the time were noted to possess a bad taste. The symptoms began in a few hours with headache, pains in the side, difficulty in swallowing, salivation, impaired vision, and retention of urine. The gait became staggering, deglutition impossible, and speech difficult and indistinct; paralysis of the right side of the face, including dilatation of the pupil and ptosis of the right eyelid, followed. Finally, cyanosis set in, salivation ceased, likewise respiration, while the heart continued to beat for about two minutes. The nature of the poison in this case was not established.

Lobsters.—Similar intoxications have been induced by lobsters and crabs. Jaksch cites an instance where an entire company partook of lobsters without any ill effects, but the remnants, which were eaten next morning by a family, caused severe illness and two deaths, the early stage of decomposition clearly giving rise to poisonous products. Another illustration is afforded by Georgii, where a number of young people ate a mayonnaise made from canned lobsters. The symptoms

were nausea, vomiting, much pain, severe headache, small rapid pulse, and a slightly sub-normal temperature. Urticaria, eye symptoms, or paralyssis, did not appear

POISONOUS MEAT.

The earliest recorded observations regarding poisonous meats were made on sausages, the wide use of which, especially in Germany, frequently led to extensive outbreaks. It became customary to speak of the "sausage poison," and the condition itself was designated as Botulism, or allantiasis. A better knowledge of the conditions leading to the production of poison in this food has resulted in a lessening of such occurrences, so that at the present time they are rather rare. The sausage is not the only meat food which may acquire poisonous properties. Every kind of meat is subject to the same changes, and if these are more frequent in the sausage it is merely because of the method of preparation and the conditions of keeping.

The question of a physiologically poisonous meat, as in some fish, and the possible presence of metals can be passed by in view of their very infrequent, if not altogether doubtful, occurrence. Similarly, the ill effects from the eating of meat infected with animal parasites, such as trichina and cysticerci, need no special attention here. After eliminating these, the entire phenomenon of poisonous meat resolves itself into the presence of bacteria and their products.

The infection of meat may result in one of two ways: First, the animal may be perfectly healthy and, when slaughtered, yield flesh entirely wholesome and free from bacteria. Such meat can acquire poisonous properties only by the introduction of bacteria from without, by contact with unclean utensils, vessels and the like. The chopping-up of meat obviously favors the spreading of organisms through the mass. Under suitable temperature conditions, the bacteria thus introduced multiply sufficiently to give rise to poisonous products, and, as a result, what was wholesome meat in the beginning, may now be positively injurious. Obviously, under these conditions various species of bacteria may be met with, and among these may be some which are true saprophytes, such as *Proteus vulgaris* and *B. botulinus*. The colon group is most frequently represented.

A second source of infection arises when the animal is diseased at the time it is slaughtered. In such a case, a specific pathogenic organism is present, more or less widely distributed in the tissues or organs, and, for that reason, the fresh meat may be toxic, or, at all events, it readily becomes so on keeping. Poisoning from such a source may not only partake of the nature of an intoxication but may also develop into an actual infection. Abundant evidence has been brought forth during the past few years to show that many forms of gastro-enteritis are really food infections, and that poisonous meat plays a very important part in their etiology. Such facts have been adduced not only with reference to summer diarrhœas but also in regard to paratyphoid infections. A large number of closely related organisms have been isolated from such poisonous meat, and, so far as known means of differentiation is concerned, they are not to be distinguished sharply from the *B. paratyphosus*.

With reference to the chemical products elaborated by the bacteria in either form of poisoning, very little is known, except in a general way. The old view that such intoxications were due to ptomaines is no longer tenable, and such basic products necessarily play an insignificant or very secondary role. The real poisons are essentially of the same character as those of the pathogenic bacteria. They may be divided into two groups according to their behavior to heat. Thus, in the case of *B. botulinus*, a soluble toxin is produced which is easily destroyed by boiling, and in this respect it resembles closely the toxin of tetanus. In the case of the *B. enteritidis*, the soluble products are not materially affected by boiling, and, hence, meat containing such may still be injurious even after it has been cooked. The presence of poisonous products in meat is not necessarily indicated by changes in taste or odor. In fact, in the majority of instances, such food is in an apparently perfect condition, and it would seem as if marked decomposition favored the destruction of the poisons formed during the early stages of bacterial action.

Notwithstanding that many different species of bacteria are concerned in the formation of such poisonous products, it is quite impossible to draw sharp differences clinically between the various intoxications. Two forms, however, are sharply contrasted. In the first the central nervous system is affected and the symptoms are therefore characteristic and well marked. Owing to the frequency of this type among the recorded cases of sausage poisoning, Van Ermengem designated it as true botulismus. In the second form of intoxication, the symptoms are gastro-intestinal. They may be of a mild type and of short duration, or of a more severe character merging into an actual infection. Such food poisonings, according to Trautmann, represent the highly acute, whereas paratyphoid fever represents the subacute, form of an infection etiologically due to one and the same factor.

Botulismus.—This term, originally employed to designate all forms of poisoning caused by sausage, is here used in the sense given by Van Ermengem—namely, a specific intoxication due to *B. botulinus*. This organism was first isolated by him, in 1895, from poisonous ham. Kempner obtained it from the faeces of a hog (1897); and in 1900 it was found, a second time, in ham by Römer. More recently (1904) it was isolated from poisonous canned beans, by Landmann. The presence of the organism in faeces, as well as its close resemblance to the tetanus bacillus, would indicate that its natural habitat is in the soil, which readily accounts for its presence in the canned beans mentioned. On the other hand, the organism can hardly be said to have a widespread existence in nature, since in a large series of tests of soil, intestinal contents of animals, etc., Van Ermengem obtained negative results.

The outbreak studied by Van Ermengem¹ occurred at Ellezelles, in Belgium, in 1895, and affected fifty persons, of whom three died. Inquiry showed that the poisoning was due to eating one ham. The flesh of the hog at the time of slaughtering was eaten without any ill effects. Moreover, the other ham, although in a decidedly decomposed state, was eaten with like negative result. This non-poisonous ham was in the same cask as the other, which was, however, on the bottom, immersed

¹ *Zeitschr. f. Hygiene*, 1897, 26, 1.

in a weak brine. A layer of pieces of fat separated the two hams, the lower one being covered by the brine while the upper was not, and being thus exposed to the air, it underwent ordinary putrefaction. The poisonous lower ham was obviously under anaërobic conditions, and the bacterial changes which occurred were of a different type from those in the one above. It was not putrid, but had a sharp odor like that of rancid butter, and though somewhat macerated it was otherwise of good appearance. The taste was said to be bad by those who partook of it.

The symptoms which followed the eating of the suspected ham were those of the typical sausage poisoning. The onset was rather late, the first symptoms coming on from twenty to twenty-four hours, and in some thirty-six hours, after the meal. Nausea, gastric pains, and vomiting were the effects first noted. In two instances there was diarrhœa, while in the others there was obstinate constipation, and retention of urine. Visual disturbances developed in from thirty-six to forty-eight hours in all cases. The patients complained of a fogging of the eyes and were soon unable to recognize persons about them. More or less marked diplopia came on. At the same time there was observed a marked dilatation of the pupils with complete loss of reaction to light, ptosis of both eyelids, and a peculiar stony stare. There was a sensation of burning thirst and strangling; the swallowing of solid food and even of liquids was difficult and led to choking attacks. The mucous membrane of the mouth, nose, and pharynx, was strongly reddened and covered with a thick viscid secretion which caused violent attacks of coughing, and even of suffocation. In some there was suppression of salivary secretion, and the mucous membrane was dry and shiny. The voice became dull, and complete aphonia was not infrequent. Extreme muscular weakness was general and persisted for weeks. Notwithstanding these severe symptoms the respiration and circulation were unimpaired. The pulse never rose above 90 and the temperature remained normal. Recovery was slow, extending over several weeks and even months. In the fatal cases collapse, dyspnœa, coma, or wild delirium, were observed shortly before death. Autopsy showed a marked hyperæmia of the organs and fatty degeneration of the liver.

The *B. botulinus* was isolated from the spleen of one of the patients. The same organism was found in large numbers, though irregularly distributed, in the poisonous ham. It was also obtained from the organs of animals inoculated with suspensions of the latter. Van Ermenegem showed that the organism was essentially a saprophyte and incapable of multiplying to any extent in the body. The symptoms, therefore, are not those of an infection but rather of an intoxication, due to the introduction of the toxin produced by the germ in the meat, or culture.

The ham which produced such marked effects in man was also very poisonous to smaller animals. Rabbits were found to be particularly susceptible and 0.5 Cc. was sufficient to cause death in from six to ten hours; while even 0.001 Cc. per kilogram weight was fatal. Assuming that man possessed the same susceptibility as the rabbit, the calculated fatal dose for a full-grown person was 0.03 mg. When this amount is compared with the fatal dose of a purified tetanus toxin, which Brieger and Fraenkel estimated to be 0.13 mg. for an average man, it will be seen that the toxin of *B. botulinus* is not inferior to the latter. The toxin,

or active poison, in the ham was soluble in water and could be readily filtered through porcelain. Like the toxins of diphtheria and tetanus, it is gradually destroyed by light and heat; on exposure of the solution at 70° C. for an hour, the toxicity was markedly weakened, and at 100° it was promptly destroyed. The toxin dialyzed rather slowly and resisted putrefaction. Acids appeared to have no effect, while, on the other hand, the addition of sodium hydrate destroyed it in a few minutes. The toxin is insoluble in alcohol and in ether; like that of tetanus, it is fixed by brain tissue; that is, a mixture of the two can be injected without causing ill effects. By injecting the toxin subcutaneously into goats, Kempner was able to produce active immunity. Moreover, the serum of the immunized goats possessed marked antitoxic properties, both as a preventive and as a curative agent. The experiments, however, were limited to animals such as cats and guinea-pigs.

Decomposed Meats.—While botulism as just described, strictly speaking, is included under this head, still it seems best for the present to reserve this designation for the more common decompositions of meat which in the beginning was perfectly wholesome and did not come from a diseased animal. In the ordinary putrefaction of animal foods, poisonous products are not necessarily formed, as is seen from the relative absence of ill effects after eating “high” game, cheese, and the like. The custom of eating fermented, in reality thoroughly putrid fish, described by Mörner for Norway, holds true for many parts of the world. Actual poisoning from such decomposed foods is of very rare occurrence.

The bacteria which have been noted in connection with such poisonings are of the *Proteus vulgaris* and *B. coli* type. The part played by the *Proteus* in fish poisoning has been discussed. Levy, in 1894, isolated a *Proteus vulgaris* from the vomited matter, stools, and from an ice-chest in which the infected food was kept. A larger outbreak was studied by Wesenberg, in 1897, in which sixty-three persons were affected by eating the meat from a cow which was slaughtered on account of illness. From the more or less decayed meat he isolated *Proteus vulgaris*. Silberschmidt obtained from a poisonous sausage, in 1899, cultures of *B. coli* and *Proteus vulgaris*. The following year Pfuhl examined a “beef sausage” which apparently was responsible for the illness of eighty-one soldiers. From this material, cultures of *Proteus mirabilis* were obtained. Schumburg also obtained from a sausage a *Proteus* culture. The sausage itself was poisonous to rats and mice on feeding; so also was meat infected with the isolated culture.

Obviously the decomposition of meat products may be induced by other kinds of bacteria. Thus in a recent instance in Michigan about fifteen persons became seriously ill from eating poorly cured bacon. An examination by the author showed that the meat was permeated by a large coccus which was highly toxicogenic to animals.

Diseased Meat.—Under this head will be considered those intoxications which are due to the eating of meat derived from a diseased animal. They constitute by far the most common form of meat poisoning and are characterized by more or less severe symptoms of gastro-enteritis. The causative agent may be said to be any one of a group of related organisms which show close affinity on the one hand for the colon bacillus, and on the other for the hog-cholera bacillus. In other words, these intoxica-

tions represent a group of closely allied diseases which it is difficult to differentiate one from another.

The symptoms may come on at once, but are usually delayed for six to twelve hours. Nausea, vomiting, colicky pains, profuse diarrhœa, and prostration are nearly always present. At times there is erythema and urticaria followed by desquamation, especially of the palms and soles. Albuminuria and catarrhal pneumonia are also met with. The mortality is much less than that of botulism. Autopsy usually shows marked gastro-enteritis of a hemorrhagic nature, an enlarged spleen, and congested organs.

Infections of this kind have followed the use of divers meats, especially beef, veal, pork, and horse-flesh. The use of chopped or minced meat, sausages, pork-pies and the like, is more often followed by poisoning than is the use of the whole meat, for the reason that the method of manipulation ensures the thorough dissemination of the organisms through the mass. In such cases the animals are often suffering from a septicæmia of puerperal or traumatic origin, or from intestinal infections. The ill effects usually follow the eating of raw or imperfectly cooked food. In some instances, however, even when the food was thoroughly cooked intoxication resulted owing to the presence of poisonous products which were not destroyed by heat. The common impression that boiling will destroy the poisonous properties which a food may have acquired does not always hold good, as has already been shown under mussel poisoning.

Although poisoning from meats was noticed at an early date and frequent attention called to it, an exact inquiry was possible only after the methods of bacteriological study had been perfected. The first attempt to work along the new lines was made by Gaffky and Paak, in 1885, in connection with poisoning caused by sausage made from horse-flesh. More than eighty persons developed gastro-enteritis and one death resulted. The evidence indicated that the horse was diseased. Moreover, the sausage was prepared in a most careless manner, since the unused portions were found to be in an advanced state of decomposition. Macerations of the sausage caused death when injected into mice, guinea-pigs, and rabbits, and from these they isolated a bacillus which was closely related to the colon bacillus. It differed from the latter in not producing indol and in not coagulating milk, in which respect it resembled Gärtner's bacillus, if not identical with the latter. It was eventually named *B. friedebergensis* by Kruse. The fact that the pure cultures when fed to animals, or when injected, caused death, led Gaffky and Paak to consider it as the specific cause of the poisoning, although its presence in the persons afflicted was not demonstrated.

Another colon-like organism, designated as *B. morbificans bovis*, was isolated by Basenau, in 1893, from the meat of a cow which was slaughtered while suffering from puerperal septicæmia. Later on, he cultivated this same organism from the flesh of animals having perforative peritonitis, puerperal paralysis, and chronic pyæmia. This bacillus, which is highly infectious to animals, has since been studied by other workers and shown to be related to the other bacilli causing intoxication.

A similar and very interesting observation of Levy and Jacobsthal may be mentioned at this point. In an apparently normal cow the spleen was found to have a large abscess, and smaller ones were present in the liver.

They isolated from the pus a germ which the cultural and agglutination tests showed to be the typhoid bacillus. This is of importance, showing as it does the possible origin of sporadic cases of the disease. The part played by meat in the causation of paratyphoid infections is at present well recognized.

Of especial interest is the food epidemic which occurred in 1888, in Frankenhäusen. The source of the infection was a cow which was slaughtered on account of a severe enteritis. All told, fifty-seven persons became ill from eating of the meat. Some of these ate it raw, while most of them had it boiled or roasted; three partook only of the broth. The symptoms were those of a severe gastro-enteritis followed by desquamation. Convalescence was long, in the severe cases lasting for two to four weeks. Only one person, who had eaten a large amount of the raw meat, died. He was nursed by his mother who later developed the same symptoms, probably as a result of infection from the discharges. Gärtner cultivated from the spleen of the fatal case, also from the flesh and intestines of the cow, an organism which he named *B. enteritidis*. This organism resembles the colon bacillus in many respects. On feeding, it proved pathogenic for mice, guinea-pigs, and a goat. On injection, it was more fatal to rabbits, pigeons, and a canary, but not to dogs, cats, chickens, and sparrows. The injection of cultures sterilized by heat produced the same effects as did the feeding of such cultures to the susceptible animals.

This resistance of the toxin of *B. enteritidis* to boiling is a striking property, and suggests the like behavior of the products of the tubercle bacillus. The heat-resisting intracellular toxin of the colon bacillus studied by Vaughan, affords another illustration on this point.

In the following year Gärtner found a similar organism in another outbreak of food poisoning at Cotta, near Dresden. The meat in this case came from a cow suffering from an inflamed udder. There were 136 persons affected, and of these 4 died; apparently all had partaken of the raw meat. Cultures were obtained from the cow and from the bodies of 2 of the dead persons, and, though they resembled the *B. enteritidis* morphologically, they differed in being non-poisonous. Moreover, the flesh of the cow lost its poisonous property when cooked.

Gärtner's bacillus attracted considerable attention and numerous workers have since then found the same or a very closely related organism.

An apparently typical *B. enteritidis* was obtained by Van Ermengem in 1891 from the outbreak at Morseele, Belgium, in which 80 persons were affected, of whom 4 died. The flesh was derived from two calves which had a severe enteritis; one died and the other was slaughtered. As in Gärtner's case, the meat was eaten in a boiled or roasted condition, though the isolation of the germ from the liver, spleen, and intestinal contents of one of the dead, would indicate that the heat was not sufficient to sterilize the food. An identical organism was obtained from the bone-marrow of one of the calves. Feeding or injection of the cultures in mice, rabbits, guinea-pigs, and calves, produced severe and fatal infection. A monkey developed typical cholera nostras, but recovered. Although there were minor cultural differences, Van Ermengem held that it was the same as the enteritidis bacillus of Gärtner, a view which has been confirmed by the subsequent studies on agglutination.

In 1892, Poels and Dhont investigated a poisoning at Rotterdam, where 92 persons became ill after eating the flesh of an apparently normal cow. The bacillus isolated formed colonies which resembled those of the typhoid bacillus; like the latter it did not ferment lactose. The sterilized cultures were poisonous and the living ones were pathogenic for mice, rabbits, and guinea-pigs. A cow which received an intravenous injection of a culture was killed twenty minutes later, and some of the meat after being kept for three days at a low temperature was eaten by 53 persons. Of these, 15 had in a short time headache, colic, and diarrhœa. In the same year, Fischer obtained an apparently true *B. enteritidis* from a food poisoning at Rummelfeld. The same organism was also obtained by him from meat which caused poisoning at Haustedt in 1895. This was derived from an ox which was killed after suffering for two days with diarrhœa and fever. Of more than 50 people who ate of the meat, chiefly in the boiled condition, 27 became ill with severe gastro-enteritis. Recovery took place in from three to eight days. The following year Fischer again met with *B. enteritidis* in the spleen of a cow which had an inflamed udder.

The food poisoning which occurred at Breslau, in 1893, also furnished a related organism. The meat was derived from a cow which was slaughtered on account of a febrile diarrhœa, and, although condemned, was stolen and sold as chopped meat. As a result of eating the raw meat 80 persons became ill in from three to sixteen hours and, although none died, recovery was slow. Dizziness, vomiting, fever, and herpes, were noted. Kaensche isolated, from the meat and from infected mice, an organism (*B. Breslaviensis*) which was apparently identical with that found by Van Ermengem in the Morseele outbreak. The toxicity of the cultures was not affected by boiling. Johné, in 1894, isolated another enteritidis-like organism from a poisoning in Saxony. Scheef obtained apparently the same bacillus, in 1896, from sausage which affected about 150 people.

An interesting case of poisoning at Ghent, in 1895, was studied by Van Ermengem. A sausage made of pork and beef was examined by an inspector, who, on account of its fresh appearance, pronounced it unobjectionable. He himself ate of the raw sausage and others followed the example. They all became sick and the inspector died in five days. The animals furnishing the meat were not known to be sick. Cultures made from the sausage and from the organs of the dead showed a bacillus which could not be distinguished from the *B. enteritidis* or from that of Morseele or Breslau. At the same time Van Ermengem called attention to the similarity which existed between these organisms and that of the hog-cholera group, a fact which subsequent investigations have fully demonstrated.

A further instance of poisoning from pork sausage occurred at Posen, in 1896, and cultures were obtained from a fatal case by Günther. The bacillus differed from that of Gärtner in minor points only. In the same year Silberschmidt studied a Swiss outbreak caused by pork which came from diseased animals. The bacillus isolated was related to *B. enteritidis* and of hog cholera, and for that reason he inclined to the view that the flesh of animals sick of hog cholera could cause food poisoning. Pouchet also, in 1879, described a hog-cholera bacillus as the cause of a poisoning which developed and involved forty-eight persons.

Since 1898 the agglutination test has been used in identifying the causative organism in food poisonings. Thus, in an outbreak of gastro-enteritis at Aertryck, in Belgium, de Nobele isolated an organism which agglutinated with the serum of the sick persons even in a dilution of one to four hundred. The sera from other diseases and from normal persons had no agglutinating action on this bacillus. Unlike typhoid serum which retains its agglutinating action for a very long time, the sera of the poisoned persons lost their agglutinating power in a few weeks. Such sera also agglutinated typhoid bacilli more readily than does normal serum. The sera, however, agglutinated in greater dilution (Aertryck) than the typhoid or enteritidis bacilli. The same author, in 1899, studied another case of poisoning at Brügge, caused by pork sausage. The serum from the affected persons agglutinated the bacillus isolated from the meat in even as high a dilution as 1 to 500, but it had no effect on the Aertryck bacillus. The Gärtner bacillus, however, was agglutinated by the sera, but not to the same extent as the bacillus isolated. Still more recently, de Nobele has succeeded in isolating essentially the same bacillus from the organs of persons who died at Brussels and Willebroek, after eating smoked horse-meat.

In England, the first application of the agglutination test in the study of these organisms was made in 1898, by Durham, who had occasion to investigate four outbreaks of gastro-enteritis. In the first of these, at Hatton, 185 persons were affected but the cause was not traced to meat of diseased animals. From the liver of a fatal case he obtained a bacillus which was agglutinated by the sera of the sick in varying dilutions, in some even as high as 1 to 1000. The sera also agglutinated the typhoid bacillus in greater dilution than did normal serum. The Günther bacillus, and one from a Vienna case of poisoning, were agglutinated to about the same extent, whereas the *B. enteritidis* was not clumped except by fairly concentrated sera. By making these tests upon different organisms, Durham was able to show that the epidemic was associated with, and probably due to, a variety of the *B. enteritidis*. In the three other outbreaks studied by him the organism was not isolated, but from the behavior of the sera of the sick to various bacteria it was made clear that the cause was essentially the same, that is, a variety of the enteritidis bacillus. That a meat infection was responsible, was particularly shown at Chatterton where veal pies were the undoubted cause of the illness of 57 or more persons, 1 of whom died.

In the Derby outbreak (1902), the cause was traced to the eating of pork pies. As at Chatterton, no complaint was made as to the taste or appearance of the pies. Furthermore, the more severe cases resulted from the eating of pies which had been kept several days, showing that the organisms, at first probably present in small numbers, in the interval had multiplied appreciably. About 210 persons became ill in Derby and its neighborhood and at least 4 deaths occurred. From the organs and intestines of two of the cases Delepine isolated the *B. enteritidis derbiensis*. This was said to resemble more closely the bacillus of Gaffky and Paak than that of Gärtner. The agglutination of this bacillus by the sera of the sick persons served to establish its causal relation to the epidemic. The evidence seemed to show that the hog was not sick and that the infection was of excretal origin.

Another well studied case of food poisoning is that which occurred at Neunkirchen, in 1903. Over 30 persons developed a non-febrile gastro-enteritis and 3 died. From the horse-flesh which was used as food and from the organs of 2 of the fatal cases, Drigalski isolated a bacillus belonging to this same group. The serum of the sick rapidly agglutinated this bacillus and that of Gärtner, and, to a less extent, typhoid and paratyphoid bacilli. On about the eighth day, all the sera reacted in a dilution of about 1 to 400 and one even in 1 to 4,000. Even the serum of a dog that ate the lungs of the horse and later developed profuse diarrhoea, agglutinated the bacillus in 1 to 100. The sera of normal persons had no such effect. He confirmed de Nobele's observation regarding the rapid loss of the specific agglutinating power. Thus, the maximum strength was reached in about ten days, while in about three weeks it had fallen to less than 1 to 100. The bacillus was shown to give rise to heat-resisting products; that is to say, boiled cultures proved fatal to animals.

From a similar case of horse-meat poisoning at Düsseldorf, in 1901, in which 57 persons became sick and 1 died, Trautmann was able to isolate a bacillus. This was obtained only from the spleen of the child. There was no reason to believe that the meat was derived from a sick horse, and, on the contrary, the evidence showed gross lack of cleanliness so that excretal contamination was quite probable.

In the majority of the cases of food poisoning mentioned, the fact that the food was derived from diseased animals was established. In some instances, as where the food was thoroughly boiled, the ill effects were those of a plain intoxication due to poisonous heat-resisting products. In the majority of instances, however, the food was eaten raw or incompletely cooked, and, as a result, true infection with the specific bacillus occurred. The relation of the different organisms which have been isolated from such outbreaks is important. In general they may be said to belong to the colon-typhoid group. Culturally and morphologically they offer very slight or no means of differentiation. For that reason they have all come to be regarded as varieties of the *B. enteritidis*. With the introduction of the serum reaction it became possible to draw the lines more closely and to establish degrees of relationship, not only among the bacilli of this group but also with typhoid, paratyphoid, and hog-cholera bacilli.

The serum of typhoid fever agglutinates Gärtner's bacillus almost as readily as the typhoid bacillus, which fact shows that a certain kinship exists between these organisms. On the other hand a typhoid serum of very high potency, obtained by artificial immunization, will distinguish with certainty between the two bacilli. Mention should be also made of the fact that the serum of animals immunized to the *B. enteritidis* agglutinates the typhoid bacillus though in less dilution than its own kind; moreover, it has no action whatever on the colon bacillus.

Especial importance attaches to the relation of this and the paratyphoid group of bacilli. Schottmüller's two types of the paratyphoid bacilli, designated by Kayser as A and B, present about the same variation with reference to the agglutination test as do the several types of bacteria from poisonous meat. Thus, the serum obtained with type B, as shown by Drigalski and by Trautmann, readily agglutinated the bacilli from the Aertryck, Breslau, Düsseldorf, Neunkirchen, and Posen epidemics, and had much less action on the Brügge, Ghent and Rumfleth bacilli repre-

sented by that of Gärtner. It would appear that paratyphoid infections are essentially the same in kind as the typical meat infections; and Trautmann, as a result of his agglutination tests, would recognize several varieties of the *B. paratyphosus*:

a—enteritidis, represented by Frankenhausen, Morseele, Haustedt and Hamburg.

b—Breslaviensis, represented by Breslau, Posen, Düsseldorf and Giessen.

c—Hamburgensis, represented by Schottmüller's type B.

d—Strassburgensis, represented by Schottmüller's type A.

e—morbificans of Basenau.

The probability of meat being the conveyor of the paratyphoid infection has been pointed out by Fischer. It is of interest to note that the several rat plague bacilli behave the same as the Aertryck and paratyphoid B organisms with reference to the agglutination test.

The classification of Trautmann is practically the same, as concerns the meat bacteria, as that which de Nobele had worked out several years before. From the behavior of the different bacilli toward very active agglutinating sera he divided them into two groups: *Bacillus enteritidis* and *Bacillus Aertryck*. The latter might also be called the hog-cholera type, since the two organisms react in the same way to sera. It is of interest to note that Fischer arrived at much the same grouping of the bacteria studied by him. On the other hand, Drigalski recognized that wholly unequivocal results could not be obtained even by the biological method of identification. While classifying some of the bacteria the same as de Nobele and Fischer, he brought together the Gärtner, Breslau, and Aertryck bacilli. The explanation of this error, if such it be, perhaps lies in the fact that he employed relatively weak sera for his tests. A more active serum would probably have shown differences, as in the case of very potent typhoid serum in its behavior to typhoid and enteritidis bacilli. The origin of his Gärtner bacillus, on account of this discrepancy, may be open to question.

POISONOUS MILK AND ITS PRODUCTS.

Of all the articles of food, milk unquestionably is most subject to bacterial contamination, and, for that reason, it is a most prolific cause not only of acute poisonings but also of real infections. The fact that milk is used to a large extent in a raw state accounts for all such accidents. Certainly, instances of poisoning from boiled milk are wholly unknown.

Injurious bacteria present in the milk may be derived from various sources. They may come directly from the diseased animal, as in tuberculosis; or be introduced either by the addition of impure water, or of excretal and other infected matter. It is unnecessary to consider these conditions at length, since in a sense they do not come under the ordinary meaning of the term poisonous milk. And yet, even a passing mention must be given to the part played by milk in the transmission of several diseases—for example, diphtheria and scarlet fever. Similarly, several epidemics of typhoid fever have been traced directly to its use. Above

all else, the milk bacteria are responsible for most of the gastro-intestinal disorders met with during the summer months, especially among infants; whereas the choleraic conditions observed among the older people can be traced with equal certainty to the use of other contaminated foods, particularly meats.

Apart from the real infections which have been noted, acute intoxications not infrequently occur. In such instances, the bacteria present give rise to active poisonous products of which but little is known. The poisonous ptomain which Vaughan first obtained from cheese has been found in milk on several occasions. It must not be supposed that in every milk poisoning the active agent is tyrotoxin, for such is clearly not the case. Milk may harbor a large number of different bacteria, and each of these will form its own characteristic toxin. Among the organisms which have been studied may be mentioned the virulent colon-like bacilli, the *B. enteritidis* and the *B. enteritidis sporogenes* of Klein. It will be seen that essentially the same organisms are found in toxic milk as are noted in poisonous meat. When such toxicogenic bacteria are once introduced into milk there is but one further condition necessary and that is a temperature suitable for their development. The warm weather of summer is therefore particularly favorable to the formation of poisonous products in milk.

The usual result of the growth of bacteria in milk is to cause it to sour. It is worthy of note that acute poisoning from sour milk is rather rare, while that from milk which shows no apparent change, in other words, one which has an alkaline or amphoteric reaction, is frequent. This is in accord with the known behavior of the enteritidis group of bacilli in milk which is not coagulated but rendered somewhat transparent.

In much the same way that chopped meats and sausages are particularly prone to become poisonous, it is obvious that preparations made from milk, such as ice-cream, frozen custards, and cream puffs, may become injurious though the original milk was not. A few hours of keeping under favorable conditions of temperature may so force the growth of the few bacteria originally present that the final product may be decidedly noxious. The popular notion that such intoxications are due to the presence of metals or of injurious flavoring extracts has no basis in fact.

The one product of milk which is most prone to cause poisoning is cheese. In fact cheese poisoning or tyrotoxinism claimed the attention of the early chemists as much as botulism or sausage poisoning. Various theories were propounded, but no satisfactory explanation was possible without a recognition of the part played by bacteria. The accidental introduction of toxicogenic bacteria, and their subsequent growth under favorable conditions, readily account for the phenomena observed. Inasmuch as different bacteria may take part in such changes it follows that different poisonous products may be met with, depending upon the organism at work. Our knowledge of these bacteria is far from being as satisfactory as might be desired. It has been shown by Vaughan and McClymonds that nearly all cheese contains poison-producing bacteria. Thus, the cultures from forty-nine samples of cheese were found to be pathogenic for white rats, rabbits, and guinea-pigs. The colon group was particularly well represented.

The poisonous ptomain Tyrotoxin, discovered by Vaughan, was the first definite product of this kind obtained from such cheese. More recently, Le Pierre obtained another basic substance, which, however, was not toxic. Without doubt other poisonous products are present, as in the case of other types of food poisoning and in real infections. The study of such toxins, as well as of the bacteria to which they owe their origin, belongs to the future.

POISONOUS VEGETABLES.

The highly nitrogenous animal products are particularly prone to undergo those alterations which render them dangerous to the consumer. Similar changes, however, may occur in vegetable products, though much less frequently, and, as a result, poisonous bacterial substances of different kinds may result. It has been shown that the same organisms which cause meat to be poisonous may give rise to exactly the same effects when they are introduced into vegetable food. The richer such material is in nitrogen, the more likely is it to give rise to poison production, and, on the other hand, with a large amount of sugars or carbohydrates the formation of such products is retarded, if not suppressed. A well known illustration of this fact is afforded by the diphtheria bacillus, which produces a maximum of toxin when grown on sugar-free media. As a further instance may be mentioned the changes which occur in whey and in whey proteids. In the former, as in normal milk, bacterial action is evidenced by a typical fermentation in which the sugar present is the chief substance acted upon, and consequently no disagreeable decomposition products of proteids form. By contrast, however, a solution of the milk proteids alone—or what is the same thing, a dialyzed whey—will undergo, under exactly the same conditions, a typical putrefaction.

Not infrequently, the ill effects observed in connection with plant food are due to the presence of metallic poisons. The strong acidity of many vegetables may, in canned goods, cause an appreciable solution of tin, lead, and zinc. Ordinarily the amount of these metals thus brought into solution is small and rarely plays a part in the observed intoxication. Criminal carelessness or ignorance is more often responsible for the presence of dangerous quantities of metals in foods.

A third type of poisoning from vegetable foods is due to the presence of plants which are in and of themselves poisonous. Under this head will fall the fairly well known ergot, vetch and mushroom intoxications. These must be considered in the briefest manner possible.

Ergot poisoning is practically unknown in this country, but in Europe is still occasionally met with, although not to the same extent as in former times. The condition is commonly designated as *ergotismus* and its cause is a parasitic fungus, *Claviceps purpurea*, which develops in the flowers of rye and other grains. From ergot, Kobert was able to isolate at least three poisonous substances, sphacelinic acid, cornutin, and ergotin. More recent investigations have made it probable that there are other substances present which constitute the real toxic agent. Thus, Jacoby obtained a non-nitrogenous resin, sphacelotoxin, which he regards

as the specific poison. The intoxication may have an acute or chronic course and in either type the symptoms may be nervous or convulsive, or else trophic or gangrenous in character.

Vetch poisoning, or *lathyrismus*, is a rather rare condition, met with in some parts of Europe, notably Austria and Italy, in northern Africa and in India. The vetch seed is used in the form of flour as a partial substitute for that of wheat. The eating of bread prepared from it is followed by sudden and severe pains in the lumbar region, girdle sensation, motor paralyses of the lower extremities, tremor and fever. The nature of the poison is not known but it is probably of the nature of a toxalbumose, of which ricin and abrin, the poisons of the castor bean and jecquiritia seed respectively, are well known examples.

The ill effects from eating mushrooms are due to mistaking the poisonous for the edible species. One species of the former contains the highly toxic alkaloid muscarin which, with other poisonous constituents, is responsible for the symptoms induced.

A most unusual and severe form of poisoning from vegetable food occurred at Darmstadt, where of twenty-one persons who ate of a bean salad, eleven died. The canned beans when opened had a peculiar odor but showed no marked decomposition. The symptoms, as reported by Landmann, came on twenty-four to thirty-six hours after eating. Visual disturbances such as mydriasis, strabismus, and ptosis, were the first to appear. Then followed difficult deglutition and bilateral paralyses. The pulse became greatly increased, respiration superficial, and death resulted in from five to fourteen days from bulbar paralysis. In the non-fatal cases convalescence lasted through some weeks. The symptoms, together with the almost complete absence of gastro-intestinal irritation, led to the diagnosis of botulism, caused by the toxin of the *B. botulinus*. This was confirmed by the demonstration of the toxin and by the isolation of the suspected organism. Cultures made from the salad gave an anaërobic bacillus, apparently identical with the *B. botulinus* of Van Ermengem. The presence of *B. botulinus* in meats is common enough, but this is the first time that the organism and this type of poisoning were observed in a vegetable food. Landmann endeavored to account for its presence by assuming that it was accidentally introduced with bits of meat into the can, as might easily happen about a kitchen. The fact remains that a highly nitrogenous vegetable, as the bean, may be acted upon by the same organism as is found in meats and that the resultant toxin may be fully as active as that formed in the latter.

Another striking example, apparently due to infected oatmeal, is that reported by Ohlmacher.¹ At the Ohio Hospital for Epileptics, in three days, 218 patients became ill and took to bed. The cause of the poisoning was not positively determined, but, by exclusion and elimination, it was finally decided to be a certain batch of oatmeal, which presumably had been contaminated by the dust arising by the removal of a large section of plaster from the ceiling the night before. This ceiling had been exposed to clouds of dust from a dirt road, and to the steam and vapors in cooking. The surface of the plaster harbored *B. coli* and *Proteus vulgaris* and these organisms were believed to be responsible for

¹Journ. Med. Research, 1902, 7, 411.

the poisoning. The symptoms appeared in from about six to eighteen hours. There was chilliness, especially up and down the spine, cold hands and feet; aching of the limbs, with severe headache and sense of pressure in the head; nausea, and vomiting in many cases—but not in all; pain in the abdomen, griping and cramps, and profuse watery diarrhoea. There was dizziness, a staggering gait, prostration and fever, the latter ranged from 100° to 105° F. and persisted for from four days to two weeks. The gastro-intestinal infection which clearly followed the original intoxication would very properly be termed paratyphoid.

The disease known as pellagra, or maidismus, is an intoxication caused by the continued use of damaged Indian corn. It was formerly met with in northern Italy, southern Austria and in parts of Spain, not as occasional poisonings but as veritable endemics affecting many thousands of individuals. While there is no question as to the fact that the poisoning is due to the corn, the actual cause, notwithstanding the numerous investigations which have been made, is by no means established. It is reasonable to believe that the specific toxic products are formed by the action of some bacterium on the maize which has been cut while immature and stored in a damp condition.

EXAMINATION OF SUSPECTED FOOD.

It has been customary to look to the chemist for the detection of the cause of a given poisoning. So far as a search for metallic poisons and vegetable alkaloids is necessary, the chemical methods must be used. When the action of bacteria can be excluded with reasonable certainty, a chemical examination should be given precedence, especially when the clinical symptoms point to definite substances, such as lead or arsenic. In the great majority of cases of food poisoning, a chemical examination is of no value and hence should not be undertaken, certainly not until all other methods of inquiry have failed. The reason for delaying such an examination is perfectly obvious, since the amount of the suspected food is usually small and would be completely used up for the chemical tests, if these are carried out in the beginning.

In order to avoid secondary decomposition the suspected food should be placed on ice until delivered for examination. Chemical preservatives should never be added. As soon as possible, animal experiments and a search for parasitic organisms should be made. The former serve to demonstrate the fact that poisonous properties are actually present in the article suspected. The material should be fed to animals, and, if necessary, introduced into the stomach by means of a tube. In such feeding experiments, it is well to bear in mind that the action of the poison is more pronounced when the stomach is empty. Macerations of the material in sterile water should be injected into other animals, and in either case, if they die, the indication is that bacteria or their products are probably present. In that event the experiments should be repeated with macerations which have been passed through a Berkefeld or Pasteur filter; also with such after boiling, in order to demonstrate the presence of a soluble toxin, or of heat-resisting products.

At the same time cultures should be made under aërobic and anaërobic conditions, and grown at the temperature of the room as well as that of the incubator. Litmus-colored sugar media should be employed if possible. The cultures thus obtained are to be compared with those isolated from the animals. Of special importance is the application of the agglutination test to the organisms thus isolated, for, if the serum of the poisoned person has a selective action on the germ found, it is conclusive evidence of the relation of the latter to the outbreak. An examination for animal parasites, such as trichina, should not be omitted if pork is present in any form in the food under examination.

Treatment.—The treatment in food poisoning must necessarily take into consideration the cause, for it is obvious that the metallic and physiological poisons, as well as the infections due to animal parasites, must be distinguished from the intoxications and infections due to bacteria. As in the infectious diseases, prophylactic measures are of primary importance, since with proper inspection of food products much can be done to restrict the consumption of improperly preserved food or such as is derived from diseased animals. Thorough cooking, while it suffices to destroy bacteria, does not always, or even as a rule, destroy their chemical products and hence cannot be relied upon exclusively.

In the severe intoxications with rapid onset, as those due to shell-fish, free lavage of the stomach should be used as early as possible and followed by a brisk cathartic, such as calomel, gr. ij (gm. 0.13), followed by a saline. Indeed, it is hardly necessary to emphasize the importance in all food poisonings of removing the toxic material by lavage, purgatives, and diuretics except in cases of collapse where stimulants may be required. In the very acute cases, where death occurs rapidly, there is little that can be done except to employ symptomatic treatment. In the more protracted cases, accompanied with paralyses due to the toxin of the *Bacillus botulinus*, artificial feeding may become necessary, and, if possible, the antitoxic serum for this form of poisoning should be employed, though the results are not very encouraging.

As the more common food poisonings represent true bacterial infections of the intestinal tract, the use of antiseptics such as calomel, salol, and like agents is indicated. Opium or morphine may be used to check excessive diarrhœa except in threatened collapse, and the vomiting may be allayed by ice. A liquid diet consisting chiefly of sterile milk and albumen water is advisable. In the more strictly para-typhoid infections the diet and treatment is the same as in typhoid fever.

CHAPTER XII.

SNAKE VENOMS.

By HIDEYO NOGUCHI, M. D.

Classification of Poisonous Snakes.—The general division of the animal kingdom known as the class Reptilia contains as a subdivision the order Ophidia, comprising all forms of snakes. This is divided into two suborders, Ophidia colubridæ and Ophidia viperidæ. The suborder Colubridæ contains, besides numerous poisonous snakes, a large number of harmless ones; both are alike in general appearance. All members of the suborder Viperidæ are poisonous. The only distinction between the poisonous and non-poisonous snakes is the presence in the venomous species of poison-glands and of poison-fangs, with teeth especially adapted for injecting the poison.

The poisonous Colubrines, Colubridæ venenosa, can further be divided into two groups by the anatomical differences in their teeth. The first group is called Opisthophidia and is characterized by the presence of one or more series of long, mature poison-fangs in the back of the mouth, while in the front, two smooth, non-grooved teeth are present in the upper jaw. This group contains three families; *viz.*—

Dipsadomorphinæ, with the nostrils situated at the sides of the head and with a strongly built mouth.

Elachistodontinæ, with the rudimentary teeth situated on the os platinum and os ptergoideum in the back part of the jaw. Nearly all snakes belonging to this division are poisonous, but their venom is so weak and the position of their poison-fangs so unfavorable, that they are scarcely dangerous to human beings.

Homalopsinæ. The nostrils are valvular, and are situated on the upper part of the snout. The eyes are small, with vertical pupils. They are absolutely aquatic and viviparous. More than twenty different species inhabit the rivers and estuaries of the East Indies and of the northern part of Australia. Some of them resemble the Hydrophinæ and swim far out into the sea.

The second group, Proteroglyphia (with grooved teeth), is the most important among all the colubrines, as they are furnished with strong fangs, provided with a frontal groove passing along their entire length, situated in the anterior part of the upper jaw; the bases of the teeth are connected with the exits of the excretory ducts of the poison-glands, which are often highly developed. To this group the following two families belong:

Hydrophinæ, sea-snakes, with the flat, oar-like tail. The head is more or less compressed at the sides. The eyes as a rule are small and have round pupils; the nasal shield is on the edge of the upper lip, which has two notches.

Elapinae, land-snakes, with cylindrical tail, smooth or wedge-shaped scales, and richly colored. Some of them, the Najas, when excited or surprised, can spread their necks until they assume a parachute shape; this expansion extends as far as the first ribs; in that case the neck appears to be larger than the head. They are found throughout Asia, Africa, and North and South America; all snakes inhabiting Australia belong to this family.

The suborder Viperidae, comprising the viperine and crotaline snakes, is distinguished chiefly by the triangular head and a stout body with short tail. The facial bones are movable; the jaw is short and has a joint with the os pterygoideus externus and bears on each side a strongly developed poison-fang, behind which are a number of reserve teeth, destined to come forward and to take the place of the principal fang, when the latter is broken or falls off at the time of shedding. The poison-fangs are not grooved as in the colubrines, but are traversed by a canal. Hence the Viperidae are also called Solenoglyphia (with tubular teeth). The upper end of the canal of the fang meets the exit of the duct of the poison-gland, while the lower opens near the point on the anterior surface of the teeth. The point of the fangs is extremely sharp. The other teeth in the mandibles are small, curved, and solid, and do not conduct the poison. Members of this suborder abound in Europe, America, Asia, and Africa, but not in Australia. This suborder is further divided into two families:

Viperinae, vipers, which have a very broad head with a small shield and scales, with, however, no pit between nose and eyes. The pupil is vertical.

Crotalinae, pit-vipers, which have a very broad head imperfectly covered with scales and are characterized by the presence of a deep depression or pit between the nostril and eye on each side of the head. Some of this family have, at the end of the tail, a series of flat horny rings graduated in size; the shaking of these rings, if the snake is excited, produces the sound from which the name of rattlesnake is derived.

Geographical Distribution of Poisonous Snakes.—The geographical distribution of the snakes in general is mainly of interest to the naturalist, but the possibility of a specific antiserum therapy makes it necessary to include a knowledge of the geographical distribution of poisonous snakes in a discussion of snake venom from the medical standpoint.

America.—*Colubridae*.—Most of the colubrines of America belong to the family Elapidae, especially to the genus Elaps. Many are called by the general name of coral-snake, but the real coral-snake, *Elaps corallinus*, is found in the forests of Brazil, Venezuela, Columbia, Guiana, and Florida. They are alternately striped with about twenty-five black and bluish-white rings on a red background. The length does not exceed three feet. They live among the withered leaves in the woods. Their poison-fangs are small and are situated at the back of the jaw, rendering their bite less dangerous. The venom itself is very powerful. *Elaps fulvius*, the harlequin snake, and *Elaps eurycanthus* abound in Arizona and the southern states; they are found even at the height of 6,000 feet. They may be often fatal to man notwithstanding their small size.

Viperidae.—The Viperæ, true vipers, are not found in America, while the family Crotalinae, pit-vipers, are very common.

The Crotalinae are divided into three genera, *Crotalus*, *Lachesis* and *Ancistrodon*. They are large and very vicious, and their venom is very powerful.

The Crotalus.—This genus lives only in America, spreading over Brazil, Texas, North and South Carolina, Florida, California, and even as far north as New York. The majority of this genus are provided with horny rings at the end of the tail, which produce the well known rattling sound. *Crotalus adamanteus*, the diamond-back rattlesnake, is the most famous species and is found in Florida and the neighboring states. They often grow over seven feet long. *Crotalus durissus* abounds in the southern states of North America and in Mexico, while the *Crotalus horridus* is found in South America, chiefly in Brazil, where it is called by the name of Boiquira. Both of these last named are the real *Crotalus* and are far smaller than their allied species, *C. adamanteus*.

The Lachesis.—The dangerous species belonging to this genus are, the fer de lance, *Lachesis s. Bothrops lanceolatus*, and the Jararaca of Brazil. They caused an annual loss of nearly two hundred human lives among the sugar planters in St. Martinique. The Surucucu, bush master, is also dreaded by the colonists in Brazil. The *Lachesis atrox*, so-called Laboria, abounds in Guiana, Brazil, Paraguay, Uruguay, Argentine Republic, and Buenos Aires. It has a short tail, the end of which is somewhat horny in nature, although there are no rings.

The Ancistrodon.—This genus is represented by the following venomous species: *Ancistrodon piscivorus*, water moccasin, and *A. contortrix*, copper-head snake. The former species is found in the tropical as well as the temperate regions and is much feared by the rice planters of Florida. Its length is about three to four feet, and it has a powerful venom. The copper-head snake is much smaller than the water moccasin but its venom is equally poisonous.

Europe.—There is in Europe only one poisonous genus, *Vipera*, which is represented by various species. *Vipera berus* is the most common species and spreads over all northern Europe, mountainous regions of central Europe, northern Italy, Spain, and Portugal. The vipers of Europe are small and seldom exceed two feet in length.

Asia.—The tropical regions of Asia have many dangerous snakes. The most dangerous among them is the famous cobra de capello, *Naja tripudians*.

Among the Colubrids the following sea and land-snakes are found:

Hydrophinae, Sea-snakes.—A large number of varieties are found on the coast, where they live in colonies. They are all poisonous and vicious, and do not come on land as a rule; when they are taken out of the water, their motion is very slow, although they swim swiftly. They float on the surface of the ocean and can dive very deeply, by virtue of the large capacity of their lungs. They give birth to living young.

Elapinae, land-snakes, comprise most of the dangerous varieties of India and Indo-China. The genera, *Bungarus*, *Naja*, and *Callophis*, are found there.

Bungarus fasciatus and *B. cœruleuse* are very common, and they reach a length of about three to five feet. The back is compressed like a wedge. They are less dangerous than the *Najas*, as their fangs are smaller.

Naja tripudians, cobra, is the best known venomous reptile, which has a pattern resembling a pair of spectacles across the back of the neck. It spreads all over the tropical zone of Asia, extending from the

southern part of the Caspian Sea to the southern part of China; and is most common in India, Burma, and the Malayan Archipelago. The *Najas* are oviparous and lay about twenty, soft-shelled, elliptical eggs the size of a pigeon's egg. They are not afraid of man and will hunt for rats and birds after sunset, in the human habitation. They swim well and live near running water.

The *Callophis*, *Hemibungarus*, is small and measures only two feet in length. It is sluggish and nocturnal, and, while it has never been known to bite man, its poison is strong for animals.

Viperina, *Vipers*.—In India and Burmah there is found a large, richly colored viper, *Daboia russelli* s. *Echidna elegans*, which attains the length of nearly six to seven feet.

Lachesis, *Trimeresurus*.—It lives in northern India, Tibet, and also in the Philippine Islands. In Japan, namely in the Riukiu Islands, there is another dangerous species, *T. riukiuanus*.

Africa.—*Colubridæ*.—*Sepedon hæmachates* and *Sepedon rhombeatus* are similar to the *Naja* and can spread their cervical ribs when excited. The latter species is found everywhere in equatorial and southern Africa. The natives believe that it can throw its venom more than three feet and if it should touch human eyes the sight would be destroyed. But in reality, it causes only a slight conjunctivitis.

Closely allied to the above species there is the *Naja haje*, *aspis* or Egyptian cobra, which often reaches a length of six feet. This species is very common in Egypt and is used by the snake-charmers; it was once worshipped by the ancient Egyptians and its picture is to be seen in the old buildings.

Viperina.—This family is well represented. In the north of Africa, *Vipera cerastes*, horned viper, and *V. ammodytes*, while in equatorial districts the *Bitis* (*Vipera*) *arietans*, puff adder, are found. The last named reaches a length of about five feet, and springs into the air before biting. According to the natives it can jump high enough to reach a rider on horseback. The Hottentots hunt this viper to get its head, from which they extract the poison, and after mixing it with certain plant juice, use the mixture for their arrow-heads.

The *Rhinoceros* viper, *Bitis gabonica*, inhabits Gabon district and vicinity of the River Ogowe; it is brownish-red in color, sluggish, and does not bite man unless molested. Its poison is powerful.

Cerastes, or horned viper, has two small, soft, horn-shaped growths near the anterior edge of the head. It is quick in motion and very dangerous for the bare-footed Arabians, who are often fatally bitten. The Sahara, Algeria, and Tripolis, is their home.

Echis carinata, pyramid viper, invades the houses of the Egyptian villages.

Australia.—*Colubridæ*.—The poisonous snakes of this continent belong to the *Colubrinae* and are peculiar to this land. The more important ones are: *Pseudechis*, *Denisonia*, *Hoplocephalus*, and *Acanthophis*. The head of the *Denisonia* is square and has curved teeth situated on the elongated part of the upper jaw. The most common ones among them are *Pseudechis porphyriacus*, black-snake, and *Hoplocephalus curtus*, tiger-snake. The black-snake can reach a length of five feet and its bite is very dangerous. *Acanthophis antarctica* s. *cerastinus*,

death-adder, is a short reptile with decorative pattern and abounds near Sydney.

No viperine snakes are found in Australia.

Oceania.—The Sunda isles and Papuasias are rich in the poisonous snakes, which are similar in species to those found in Asia. The sea-snakes are quite abundant.

Poison Organs.—The poison-fangs are hollow or grooved teeth, supplied with a canal, or furrow, running the entire length of the tooth. The fangs of the *Proteroglyphia* (with grooved teeth) and of the *Solenoglyphia* (with tubular teeth) are immovably attached to the upper maxillary bone, and completely covered with a broad prolongation of the gingival membrane; this, at the same time, hides the reserve fangs in their varying stages of development. These are two to six in number, and grow out in the place of the mature fangs, in case the latter are damaged or shed. The upper maxillary bone is quite movable and, when drawn backward, erects the fangs to a vertical position; when at rest they lie horizontally. At the same time, the contraction of special constrictor muscles squeezes the poison-glands, the excretory ducts of which open into the canal at the base of the fangs.

The size and shape of the poison-fangs differ according to the species. Thus, the *Viperinæ* have longer and sharper teeth with more pronounced curvature, which causes a deep wound. On the other hand, the fangs of the *Elapinæ*, and especially of the *Hydrophinæ*, are much shorter; the poison of the latter is, however, much more dangerous than that of the former. The fangs can attain, as in *Bothrops* and *Crotalus*, a length of 25 mm. The narrow, slit-like opening of the canal of the fangs on the *Solenoglyphia* is situated at the anterior end,—on the convex side,—of the tooth. These differences, together with the arrangement of the other numerous small teeth, enable one to determine the species.

The poison-glands are similar in structure to the salivary glands, and occupy a wide space between the muscles below and behind the eyes, on both sides of the upper jaw. In the *Naja* the size of the gland reaches that of an almond. The gland is covered with a capsule: fibers from the masseter muscle pass into the interior of the gland, and, on constriction, force the poison out of the gland. The secreted venom accumulates in the acini, and in a sac formed by a dilatation of the mucous membrane of the duct. The walls of this sac, also, contain a thin layer of muscle fibers from the same muscle, which form a constrictor at the exit of the ducts.

The non-poisonous snakes, as well as the poisonous ones, possess parotid and supralabial glands; the supralabial glands secrete a poison. The non-poisonous snakes have no fangs but the secretion of the venom seems to be indispensable to the function of digestion.

The histological process of the secretion of venom from the gland cells can be divided into two phases,—the development of the cell nucleus, and the action of the cell protoplasm. So-called “venogen” granules,—uniform, round granules,—are produced from the nuclear chromatin; this transformation can be followed by the varying staining reactions of the chromatin granules during the process. An exomösis of dissolved nuclear substance also occurs, forming stored, or “ergastoplasmic” venogen. The nuclear membrane takes an active part in the secretion of both these forms of venogen. The venogen granules and the stored venogen dis-

appear during the physiological activity of the cell, the venogen granules (characterized by their affinity for Unna's blue, safranin, and fuchsin) being converted into the venom granules, which are eosinophilic.

The act of striking consists in drawing the head backward, opening the mouth widely, erecting the fangs to a vertical position, and exposing them by drawing back the gingival sheath of the fangs; the snake strikes very quickly and immediately draws its head back. At the moment of striking, the jaws are closed and the glands, together with the venom-sacs and the excretory duct, are compressed so forcibly that the venom flows out in a stream. The muscles concerned are: *M. masseter*, *M. temporales*, *M. pterygoidei interni et externi*.

The amount of venom yielded at one time by a snake, either at a single bite or by squeezing the poison-glands, is very variable. It increases, however, in general, in proportion to the size of the snakes, although this rule cannot be applied to the sea-snakes, which secrete an amount which is small compared to their size. The progressive failing of their health in captivity causes a decrease of venom, both in quantity and in toxicity; especially is this the case where the snakes refuse to take nourishment, and are subjected to repeated extractions of venom. While it is very important to determine the exact quantities of venom yielded at a single bite, the data bearing upon the subject are very unsatisfactory. According to Lamb, the amount of venom thrown out voluntarily by a snake is larger than that obtained by the forcible squeezing with the fingers.

The following table will show the amounts of venom yielded, at one time, by certain important snakes. The venom was collected by squeezing the glands, and the weight estimated in a dry state.

<i>Naja tripudians</i> . 0.254 (Cunningham), 0.231 (Lamb), 0.373-bite (Lamb), 0.249 (Rogers).	<i>Pseudechis porphyriacus</i> . 0.094-0.046 (Smith).
<i>Naja haje</i> . 0.048 (Calmette).	<i>Enhydrina</i> . 0.127 (Calmette).
<i>Hoplocephalus curtus</i> . 0.055-0.017 (Smith).	<i>Lachesis, fer de lance</i> . 0.127 (Calmette).
<i>Ancistrodon piscivorus</i> . 0.0094-0.0023 (Rogers).	<i>Crotalus adamanteus</i> . 0.309-0.179 (Flexner & Noguchi).
0.18-0.125 (Flexner & Noguchi).	

Physiological and Chemical Properties of Venom.—All snake venoms are viscid fluids which vary in color from the palest amber to a deep yellow; they look alike when in the fresh state. The amount of pigment varies in the venom of different snakes, and repeated extraction of venom from the poison-glands causes a decrease in color and quantity. When fresh venom is allowed to dry slowly it cracks into small, yellow, very fragile, transparent, or translucent, particles, which resemble an aggregation of crystals.

A number of floating bodies are always seen in fresh venom when examined under the microscope. These suspended bodies consist principally of fine, ovoid, highly refractive granules, which are of albuminoid nature. A few epithelial cells, fat globules, and occasional leukocytes occur in fresh venom. The chlorides and phosphates of calcium, ammonium, and magnesium, are present. The specific gravity varies between 1,030 and 1,070, the Colubrine venoms being lighter than the Crotaline. The loss of weight on drying varies, and it is more marked in the Colubrine venom, 65 to 80 per cent. (Calmette), but is comparatively slight in the Crotaline,—25 per cent. (Mitchell) to 35 per cent. to 50 per cent.

(Flexner-Noguchi) with *Crotalus adamanteus* and *Ancistrodon piscivorus*,—while the loss is estimated to be 33 per cent. (C. J. Martin) with the Australian snake venoms.

The reaction of fresh venom to litmus is faintly acid, which is, as a rule, weaker in the Colubrine than in the Crotaline venoms.

Our knowledge of the chemistry of venom is still far from being satisfactory. Lucien Bonaparte (1843) announced that the active principle of a viper venom is a proteid, and called it viperin, or echidnin. Busk thought it a ferment similar to ptyalin. Brunton and Fayrer (1873) stated that boiling does not destroy the activity of the venom of cobra, while Gautier maintained that venom contains ptomain. Mitchell and Reichert (1886), working on the venoms of *Crotalus adamanteus*, *Ancistrodon contortrix*, *Ancistrodon piscivorus*, and Cobra, separated several active principles.

According to their studies venom contains three principal proteids—two water-soluble, and one water-insoluble, components. Of the former two, one is coagulable by heat, while the other remains in solution upon boiling. The first is venom-albumin and is not poisonous; the latter stands very close to peptone in its chemical reactions and is called venom-peptone. The water-insoluble ingredient of venom has been classed among the globulins and is called venom-globulin. Working with these two separate proteids, venom-peptone and venom-globulin, they found that the action of each constituent is different; venom-peptone is responsible for the production of œdema, putrefaction and necrosis of the tissue, while the action of venom-globulin is chiefly upon the respiratory and circulatory system; it destroys coagulability of the blood, produces ecchymosis, lowers the blood pressure, and paralyzes respiration. The venom retains its solubility and toxicity after being precipitated by absolute alcohol.

C. J. Martin succeeded in separating two active components of the venom of *Pseudechis* by filtering it through a gelatinized Chamberland filter under a pressure of 50 atmospheres. One component does not pass through the bougie and is coagulable at 82° C.; the other passes and is not coagulable upon boiling. The first produces local hemorrhage and destruction of the blood; the latter acts upon the nervous system. According to Martin and Smith, the albumoses of venom are hetero-, proto-, and perhaps deuto-albumose. They found no trace of peptone. Kanthack stated that in venom there is only one primary albumose from which other albumoses—hetero- and dysalbumoses—can be formed under certain circumstances, as by dialysis. Phisalix and Bertrand have prepared from viper venom two toxalbumins; one (echidnin) which acts locally and is easily destroyed by boiling for a short time, the other (echitoxin) is poisonous to the vasomotor system and withstands boiling.

The stability of the active principles of snake venom in a dry state is one of its most remarkable features. Mitchell preserved crotalus venom for twenty-three years; Christison, cobra venom for fifteen years, and Vollmer for sixteen years, without any marked deterioration.

The venom gives the proteid reactions,—namely, the Millon, xanthoprotein, and biuret reaction. On addition of picric acid a precipitate is formed which disappears on heating and reappears on cooling. By saturating with sodium chloride, magnesium sulphate, ammonium sul-

phate and 5 per cent. solution of copper sulphate or alcohol, the venom can be precipitated.

Heating.—The venom of colubridæ (in solution) can be exposed to a temperature of 100° C. for a brief period; 120° C. destroys its activity with certainty. The viperine venoms are much more susceptible to higher temperatures. Heating to the coagulating point is sufficient to diminish their toxicity to a considerable extent. Temperatures of 80° to 85° C. suffice to destroy the toxicity of most of the viperine venoms. After the removal of the coagulum by filtration the clear filtrate can be precipitated by alcohol but not by boiling. The filtrate from the heated colubrine and crotaline venoms is toxic, especially to the nervous system. Bothrop's venom loses its activity partially at 65° C. The higher the concentration of venom, the less injurious are the higher temperatures. The action of dry heat of 130° C. upon dried venom does not destroy its activity.

Dialysis of venom is a very slow process and it is almost impossible to accomplish this with animal membranes,—though vegetable tissue may be used with better results. Filtration through a Chamberland bougie has almost no perceivable effect upon the colubrine venoms, but it reduces the toxicity of the viperine venoms nearly one-half.

A constant electric current passed through a venom solution, which contains certain salts, will produce chlorides and ozone, and, as a result of the ozone production, the activity of the venom is destroyed. Phisalix applied an alternating current of high frequency to the venom solution,—with the view of producing a vaccine by the same process as d'Aronval and Charrin employed for preparing vaccine for diphtheria toxin,—and claimed to have obtained the same results. Marmier, however, attributed this modification of the venom to the heat produced by the current, as by using an appropriate apparatus avoiding the rise of the temperature he was not able to confirm Phisalix's work.

Light has no influence upon the dried venom. In a state of solution, venom suffers but little deterioration on being exposed to diffuse light, but is gradually weakened by exposure to the direct sunlight. Even in the dark a solution of venom undergoes a rather marked reduction in toxicity when kept at room temperature. Freezing has no marked destructive action upon venom. Radium produces a precipitate of the proteids of cobra venom and at the same time destroys its toxic properties.

The hemorrhagic principles of crotalus venom and the clotting principle of daboia venom can be made inactive by photodynamic substances. The hæmolytic principles are less affected by them (Noguchi).

Among the chemicals which are capable of destroying or modifying the toxic properties of venom, there are some which can be injected into the surrounding tissue of the bitten part in order that the still unabsorbed portion of the venom may be made inactive with the least harm to the patient, and these are: potassium permanganate 1 to 100 (Mitchell, Fayer, Lacerda, Richard, Rogers), chloride of gold 1 to 100, chloride or hypochlorite of calcium 1 to 60 or 72 (Calmette), chromic acid 1 to 100 (Kauffmann) and saturated bromine water.

A finer analysis shows that venom owes its toxicity to the presence of several active principles which are capable of producing profound alteration or destruction of susceptible tissue. The changes brought about

by the action of the active principles of venom vary in accordance with the nature and the amount of the latter, ranging from the slightest local inflammation to the complete cessation of vital functions. These toxic components are present in varying proportions in different venoms. The greater number of these principles can alone be fatal when present in sufficient quantities, and one will thus form the chief toxic principle of a venom where it predominates over the other constituents. The hitherto known toxic components can be divided into the chief toxic principles and those of secondary importance, and these are:

1. The principle which produces an instantaneous intravascular thrombosis.

2. The principle which attacks the nervous system.

3. The principle which produces the rupture of the walls of capillary vessels, causing extensive hemorrhage.

4. The principles which attack the blood corpuscles, causing hæmolysis and agglutination of the latter

5. A number of cytolytic principles for other cells.

6. The protective or hardening property upon the red blood corpuscles.

7. Loss of bactericidal property of the blood.

1. The Blood-Clotting Component of Venom.—The venom of certain snakes has a great influence upon the coagulation of blood. When in sufficiently large quantity, it produces an instantaneous intravascular thrombosis (positive phase), while, if in too small quantity to cause this change, it destroys the coagulability of the blood for a long period (negative phase). It is due to this first change that certain venoms produce an instantaneous death of the victim. The venoms which are able to bring about this sudden clotting *in vivo* are Daboia, Bungarus fasciatus, Hoplocepholus curtus, Echis carinata, Pseudechis porphyriacus, Trimeresurus riukiuanus, and Crotolus adamanteus.

Lamb has also demonstrated that the fluid plasma, or blood containing one to two per cent. sodium citrate, can be coagulated by adding a small quantity of daboia venom *in vitro*.

The symptoms due to the blood-clotting principle are sudden loss of equilibrium, violent general convulsions, and quick termination in death, which follows within several minutes. At times death may take place even in a half minute. At autopsy extensive intravascular thrombosis is found, chiefly affecting the pulmonary arteries and right heart.

2. The Neurotoxin of Venom.—Most of the venoms of the Elapidæ and Hydrophinae contain a large amount of neurotoxin, which is richest in the venom of Cobra and Bungarus. When present in large amount death may occur within fifteen minutes. In cobra-venom poisoning, death is caused, by one minimal lethal dose, within two or three days, while in the case of Bungarus venom the poisoning is to be divided into two forms, one an acute, the other a chronic form. The acute form is exactly the same as in cobra poisoning. With these venoms there are almost no local symptoms except a slight œdema and occasional ecchymosis. The symptoms are stupefaction, paralysis of limbs, accompanied by twitching of muscles, dyspnœa, and final cessation of respiration. The heart may continue to beat even for five minutes after respiration has stopped. The longer death is delayed, the more pronounced will

be the cedema at the site of injection. The chronic form is most characteristic in Bungarus venom, but has never been observed in cobra venom. Death may follow after twelve days. In the first several days there may be no marked symptoms, but after this latent period the loss of body-weight and appetite, great depression, marked muscular weakness and atrophy, and extreme emaciation, advance progressively, and the animal succumbs in a few days.

Some investigators observed the curare-like action of cobra venom upon the peripheral nerves (Brunton, Ragotzi, Fayrer, and Jacoby), while the same action is recorded with venom of a sea-snake; Rogers has found that even a strong solution of sea-snake venom does not alter the conductivity of the nerve fibers, while the end plates of the muscle, especially those of the diaphragm, are quickly involved.

With certain venoms the reflexes may disappear either before, or simultaneously with, the appearance of motor paralysis. In such cases the reflexes do not reappear after the use of strychnine, nor does a primary stimulation of the reflexes by strychnine prevent the reflex paralysis caused by venom. In some cases (rabbits, mice, pigeons) slight acceleration of reflexes can be noticed before the paralysis. Venom exerts a slight action upon the motor ganglion of the heart. In warm-blooded animals there is rapid diminution of the blood content of the right heart, with incomplete contraction. The left heart is next affected in the same manner. After the cessation of respiration, the heart stops in diastole or semi-diastole. The beating is made slow by the stimulation of the vagus centre, then through the paralysis of the cardiac ending of the vagi it becomes quicker, although the energy is gradually reduced. The consequence of this is a fall of blood pressure. Besides the anæmia of the brain, a direct action upon the vasomotor centre contributes to this effect.

The histological changes produced by moccasin venom upon the nervous system of the rabbit have been found to consist in a true acute degeneration of the ganglion cell. Most of the cells of the anterior horn of the spinal cord were normal, but a small number presented modifications which were considered to be an early stage of acute degeneration. The histological changes in the nervous system of monkeys, rabbits, rats, and pigeons, produced by the venoms of cobra and Bungarus fasciatus are similar, but the more acute action of cobra venom does not allow sufficient time for the destructive changes to become clearly marked. The best pictures were obtained in the more chronic cases of Bungarus poisoning. In these there is undoubted evidence of an acute chromatolysis involving the motor ganglion cells of the cortex, the pons, the medulla, and the cord. There is slight increase of connective tissue throughout the gray matter of the central nervous system. The histological condition is that of polioencephalitis and poliomyelitis. The clinical facts observed, such as atrophy and paralysis of the muscles, agree with the histological changes found. The muscular atrophy is probably due to functional disturbances of the trophic centres.

The action of the venom of cobra, water moccasin, and rattlesnake upon the isolated ganglion cells of certain species of Gastropod, have been followed by Flexner and Noguchi, directly under the microscope. The effect is a chromatolysis with a final complete disappearance of the cells.

3. Hemorrhagic Principles of Venom.—The most striking effect of the viperine and crotaline poisoning is the rapid discoloration and swelling of the site of injury, as well as the profuse bleeding from the wound. The extent of discoloration and swelling is variable according to the amount of venom injected, but as a rule it spreads gradually over the half of the body in which the wound was received, and the intensity steadily increases even after two days have elapsed since the bite.

A close examination of the tissue will reveal the fact that the discoloration is really due to extravasation of blood into the skin and muscles, through the rupture of the walls of capillary bloodvessels. The bleeding from the open wound may continue for a day or two and is one of the most conspicuous features of the *Crotalus* poisoning. The final result is generally a necrosis of the entire tissue affected, which may form an ulcer, or heal with a scar.

Experimentally, we can easily demonstrate the minute capillary bleeding, under the microscope, by exposing the mesentery of small animals and applying a small particle of dried venom to the membrane. It is rather difficult to follow the actual disunion of the cells of the capillary wall without staining, but when properly prepared we can see the rupture of the wall or the dislocation of the endothelial cell at the spot where the hemorrhage took place (Flexner and Noguchi). In certain fish, such as *Mustelus canis*, the cerebral hemorrhage may be clearly seen during life, when an appropriate dose of the *Crotalus* venom is given intraperitoneally. The effect of the hemorrhagic principle of venom is very quick. The susceptibility of various animals to hemorrhagin is variable, but as a rule warm-blooded animals are more susceptible than cold-blooded ones. Batrachians are least susceptible, while Cheludra are moderately sensitive to this principle. Hemorrhages may occur in any of the organs of the body and may be the immediate cause of death.

The hemorrhagins contained in different venoms vary in amount, and are not quite identical so far as their reaction to the antivenins is concerned. The oedema-producing principles of venom seem to be independent of the hemorrhagins. There are certain venoms which produce marked oedema but not much hemorrhage, such as those of daboia and cobra, although it is difficult to say whether some venoms producing strong hemorrhage contain the oedema-producing principle, as the former obscures the latter. It may be stated that the oedema-producing principle is more resistant to high temperature than the hemorrhagin.

4. Hæmolytic and Hæmagglutinative Principles.—The influence of venom upon the coagulability of blood both *in vivo* and *in vitro* has already been noted. The next important property of venom, both from the theoretical and practical points of view, is its action upon the cellular elements of the blood. Many investigators paid attention to the changes of the blood corpuscles in venom poisoning, but were unable to find any definite alteration in the cells. Of course it has been repeatedly observed that the destruction of the blood corpuscles occurs in the body, as indicated by the appearance of hæmoglobinuria, or hæmaturia, in cases of venom poisoning. But it was a matter of conjecture that there was such a definite destruction of the corpuscles by venom, until the blood was drawn directly from the vessel of a victim and allowed to

coagulate or settle, when the serum was found to contain free hæmoglobin.

The blood of a normal animal was also mixed with venom, outside of the body, in a test tube, and there the hæmolytic and discolorizing properties of venom were conclusively and quantitatively determined. The very early experiments on these properties of venom were carried out by Mitchell and Reichert, who used *Crotalus* venom; they described also the agglutinating property of that venom upon the blood corpuscles of the rabbit. While the hæmolytic and the agglutinative properties of venom were not separated at that time from one another, the recent studies indicate the independent nature of these two principles, and also the other cytolytic components, like neurotoxin, leukolysin, hæmorrhagin, endotheliolysin, etc., which are found to be present in snake venoms in varying proportions, according to the source of the venom.

The nature of the hæmolytic action of venom has been found to be analogous to the same process produced by normal or artificial serum hæmolysins, and in both cases there are amboceptors which require certain complementary substances in order to complete the solvent action. In the case with serum-hæmolysis the so-called complements or alexines act as the complementary bodies, while with snake venom not only the ordinary serum complements but also certain thermostabile constituents of the blood can activate the venom amboceptors. The thermostabile complements are found to be the substances belonging to the lipoids; and lecithin and kephalin are very suitable to activate venom. Kyes succeeded in preparing a crystalline compound of the hæmolytic principle of various venoms and lecithin. This compound (venom lecithid) is itself highly hæmolytic.

5. Additional Cytolytic Principles in Venom.—Venom contains in varying proportions a series of other active solvent agents for various cells. According to Flexner and Noguchi,¹ these are solvent agents for the cells of the liver, kidney, spermatozoa, testis, and ova, and they require certain complementary substances to perform their lytic action upon the cells. These complementary bodies, whose nature is still not definitely known, exist either in the body-juice or in the cell-body, and they are made inactive by heating to 60° C. for half an hour.

6. Protective or Hardening Property upon the Red Blood Corpuscles.—It was demonstrated by Mitchell and Stewart that, when *Crotalus* venom is employed in a strength above certain concentration, its destructive action upon the blood corpuscles becomes gradually weakened, until a limit is reached where no hæmolysis takes place.

In a mixture of equal parts of venom and physiological salt solution such a non-hæmolytic mixture will keep for a considerably longer period than the normal controls without the venom. Myers and Stephens observed the same phenomenon with cobra venom and human blood; Flexner and Noguchi with rattlesnake; Lamb with deboia; Kyes, and Kyes and Sachs with cobra venom. The last named authors tried to explain this phenomenon by the hypothesis that the introduction of too large an amount of amboceptors results in a deviation of the complementary substance, lecithin, which is present only in a limited quantity in the mixture. Noguchi has, however, shown that the corpuscles, which are

¹*The Jour. of Path. and Bact.*, 1905, x, iii.

treated with such strong venom solution, undergo a change which not only prevents the hæmolytic process under the solvent action of venom, but also changes the corpuscles so that the escape of hæmoglobin in hypotonic media, like water, does not occur. Certain hæmolytic agents, for example, saponin, tetanolysin and cobra lecithid, are without solvent action upon the corpuscles thus modified. On the other hand, alkalis and acids hæmolyse these corpuscles with readiness. According to his studies, venom forms an insoluble compound or precipitate with different constituents of the blood; the formation of such a precipitate seems to be the immediate cause of rendering the corpuscles non-hæmolysable. The precipitates produced by bringing venom and different constituents of the blood into contact are soluble in alkalis and acids, and this would explain the hæmolysis of the modified corpuscles by those chemicals. Another remarkable feature is that the corpuscles treated with strong venom solution are not hæmolyzed by a high temperature maintained for a long time, at which the controls with normal blood undergo complete hæmolysis. Among the constituents of the blood known to be capable of forming a precipitate with venom are hæmoglobin, globin, and globulins. It is of some interest to note that not all kinds of blood are subjected to this change under the influence of venom. In cases where there is no protective phenomena, it is also found that the hæmoglobin of such blood is not able to form the water-insoluble precipitate with venom.

7. Loss of Bactericidal Property of the Blood.—After the apparent recovery from the local and general effects of various venoms, there are many instances in which a secondary infection has developed. This is attributed to the loss of the bactericidal property of the normal blood due to the venom poisoning. According to later investigations of Flexner and Noguchi, the antibactericidal property of venom is due to its faculty of destroying (or rendering inactive) the bacteriolytic complements of the serum.

The fate of venom in the organism is not quite known. Some assume that it undergoes decomposition, as the blood of a venomized animal does not produce intoxication in a second, when it is transfused. Some thought it to be secreted by the urine, while still others claim to have found it in the contents of the stomach.

Toxicity of Venom.—The minimal lethal dose of a snake venom depends upon the kind of venom and upon the susceptibility of different classes of animals. The figures by different investigators do not quite agree, possibly because of differences in the source and preparation of the venom used. The minimal lethal doses per kilo body-weight for some common animals are as follows:—

Elapinae.

Naja tripudians (Cobra).

Rabbit: Intravenous injection, 0.00025–0.0005 (Calmette), 0.00035 (Lamb), 0.000245 (Fraser), 0.0007 (Elliot).

Guinea pig: Subcutaneous injection, 0.0005 (Noguchi), 0.0004 (Calmette), 0.00018 (Fraser).

Rat: Subcutaneous injection, 0.0004–0.0007 (Lamb), 0.0006 (Calmette), 0.0005 (Rogers).

Dog: Subcutaneous injection, 0.0005 (Lamb), 0.0008 (Calmette).

Horse: Intravenous injection, 0.00009 (Lamb).

Monkey: Intravenous injection, 0.00025 (Lamb).

Naja bungarus (King Cobra).

Rabbit: Intravenous injection, 0.00035 (Lamb).

Bungarus fasciatus.

Rabbit: Intravenous injection, 0.0007 (Lamb).

Subcutaneous injection, 0.0025–0.003 (Lamb).

Bungarus coerulescens (Common Krait).

Rabbit: Intravenous injection, 0.00004 (Lamb).

Hoplocephalus curtus (Tiger-snake).

Rabbit: 0.000289 (Calmette), 0.00025 (C. J. Martin).

Pseudechis porphyriacus (Black-snake).

Rabbit: 0.00125 (Calmette), 0.0005 (C. J. Martin).

Hydrophinae (Sea-snakes).

Hydros platurus.

Pigeon: 0.000075 (Rogers).

Mud-fish: 0.00025 (Rogers).

Enhydrina bengalensis s. valakadien.

Pigeon: 0.00005 (Rogers).

Mud-fish: 0.0005 (Rogers).

Rabbit: Intravenous injection, 0.00005 (Lamb).

Crotalidae (Pit-vipers).

Ancistrodon piscivorus (Water Moccasin).

Guinea pig: Intravenous injection, 0.0025 (Noguchi).

Goat: Subcutaneous injection, 0.0004 (Noguchi).

Crotalus adamanteus (Rattlesnake).

Rabbit: Intraperitoneal injection, 0.0002 (Noguchi).

Subcutaneous injection, 0.005 (Noguchi).

Guinea pig: Intraperitoneal injection, 0.002 (Noguchi).

Viperinae (Vipers).

Vipera russelli (Daboia).

Rabbit: Intravenous injection, 0.0001 (Lamb).

Guinea pig: Intraperitoneal injection, 0.0002 (Lamb).

Monkey: Intravenous injection, 0.003 (Lamb).

Vipera berus (Common European Viper).

Rabbit: 0.004 (Calmette).

For a man of 60 to 70 kilos the fatal dose of cobra venom has been reckoned by Lamb, from the experiments on monkeys, to be 0.015 to 0.0175 gm. Calmette's estimate is 0.01 gm., while Fraser puts the figure as high as 0.031 gm. Rogers considers 0.0035 gm. of the venom of *Enhydrina* to be surely fatal for a man of 70 kilos.

Certain venoms present a great difference in their fatal effects according to the mode of injection. The action of cobra venom injected subcutaneously is much slower than when injected intravenously, but the final result is the same; while the venom of *Crotalus* or *daboia* can be injected in much greater quantities subcutaneously than intraperitoneally, or intravenously.

Cold-blooded animals are less susceptible than warm-blooded; many of the invertebrates especially are not seriously or not at all affected.

The immunity of poisonous snakes to their own venoms seems to be general. They are also relatively immune to alien venoms. It is inter-

esting that the venoms of the Colubrine snakes are more poisonous to the Reptilia and Batrachians, while the viperine or Crotaline venoms are always less active upon those classes of animals.

Symptoms of Venom Poisoning in Man.—The symptoms observed in man can be divided into local and constitutional. The local symptoms consist in a rapidly appearing, inflammatory swelling of the site of bite, followed by more or less ecchymosis and necrosis, with or without pain, and often with the appearance of lymphangitis and local phlegmon. With *Crotalidæ*, when the local lesions are especially severe, there develops, besides the œdema, extensive hemorrhage and gangrene.

The constitutional symptoms are fever, cerebral and spinal disturbances, especially of the medulla, including paralysis of the respiratory centre. The motor paralysis also advances steadily. Hæmaturia, hæmoglobinuria, hæmatemesis, diarrhœa, vomiting, amaurosis, headache, vertigo, violent dyspnœa, and general convulsions are often observed. In the viperine poisoning, cold perspiration, a small intermittent pulse, and final dyspnœa are also seen. Cobra venom destroys the respiratory functions rapidly, without affecting the pupils, while the daboia poisoning is accompanied by a dilated pupil. Cobra venom causes more convulsions. Fayrer states that cobra venom kills a man without affecting the coagulability of the blood, while in a sub-acute daboia poisoning the blood remains permanently fluid. If death occurs within several minutes after the bite of daboia, extensive thrombosis is found in the pulmonary artery and right heart.

Mortality.—The mortality from snake bites is naturally greatest in those countries where poisonous snakes are more abundant and the conditions of human life favor exposure. Thus in India there is an annual loss of 20,000 human lives, or 16 per 100,000. The temperament of different species of poisonous snakes also influences the degree of danger. Thus, for example, the comparatively slight danger from rattlesnakes is due to their sluggish temperament. According to Weir Mitchell seven-eighths of all cases of rattlesnake bites will recover, as their fangs are not raised enough and the injuries are often made only by the lower teeth. On the other hand, cobra bites are fatal in from 25 to 45 per cent. of cases (Calmette). The depth and locality of the wound are important conditions; the deeper the wound the more dangerous. Wounds in the face, especially in the lips and tongue, are more dangerous than in the limbs, while bites of the fingers or toes are again very dangerous, owing to the fact that the fangs can be driven deeper in the tissue. The alleged immunity of snake-charmers to deadly Egyptian and Indian serpents is not quite understood. In some cases the poison-fangs are certainly removed; that the snake-charmer does not enjoy real immunity against the effects of the venom has been frequently shown.

The length of time which elapses before death is very variable in different venoms. The quickest fatal cases reported are two minutes in a *Crotalus* poisoning, and five minutes in a Japanese snake bite, but more frequently death occurs after fifteen minutes. In most of the fatal cases of cobra poisoning the end comes between six and twelve hours, although quite often within two hours, or even after one or two days.

As to the time of death after the bite, Fayrer gives the following statistics taken from 65 fatal cases of cobra poisoning:

22.96% died less than 2 hours after the bite,
24.53% died between 2 and 6 hours after the bite,
23.05% died between 6 and 12 hours after the bite,
9.39% died between 12 and 24 hours after the bite,
21.10% died after 24 hours.

The bite of the famous *Lachesis lanceolatus* of St. Martinique causes death generally after one or two days, and very seldom earlier than six hours after the bite. With the venom of *Trigonocephalus*, death may come after two to five, or even as late as ten days. Death after sixteen days from the bite of a *Crotalus* has also been reported. The viperine bites are not quickly fatal, but cause marked local and general disturbances, which cause death after days, weeks, or months; but when the venom gets into the circulatory system death may occur more quickly, with sudden loss of consciousness, delirium, tetanus, and trismus.

In fatal cases, when death follows after a long period, anatomical changes, such as hemorrhage and local necrosis, are always pronounced. Even in the patients that recover, local paralysis of the most diverse parts of the body may persist for a long time, together with various local manifestations on the bitten side. The sequelæ are paræsthesias of various kinds, pemphigoid eruptions, and pain.

Treatment of Snake Poisoning.—The treatment of snake bites can be divided into non-specific and specific therapy.

The non-specific treatment consists in (1) retarding absorption and (2) the removal or destruction of the free venom as far as possible. The retarding of the absorption is accomplished by the application of a ligature above the bitten part, but the ligature must be removed not longer than thirty minutes after, because of the danger of necrosis. A simultaneous opening of the fang wounds and cupping or sucking with the mouth will remove the venom mechanically. But the injection of certain chemical agents into or around the bitten spot can be made with great advantage, as definite concentration of certain chemicals can destroy the free venom without causing any serious injury to the tissue itself. Below is given a brief list of the chemicals which have been recommended by many eminent investigators and employed for the same purposes: potassium permanganate 1 to 100 (Weir Mitchell, Fayrer, Lacerda), chloride of calcium or hypochlorite of calcium 1 to 60 or 1 to 72 (Calmette), chloride of gold 1 to 100 (Calmette), chromic acid 1 to 100 (Kauffmann). These chemicals have no neutralizing action when they are injected into the vein or parts distant from the wound. They must always be injected into or around the bitten part.

As to the general or symptomatic treatment it is recommended to administer stimulants in various ways. Halford recommended the injection of 10 to 20 drops of ammonia in equal parts of water into a vein. It has a stimulating action for some time, but if the amount of venom inoculated reaches a minimal fatal dose it fails to save the life of the victim. Experimentally it has no antidotal property whatsoever.

Müller recommended the injection of strychnine, but the statistics obtained by Huxtable show that of 426 cases of snake bites, 113 were treated with strychnine, and 15 of these died, equalling 13.2 per cent. mortality. The remaining 313 had no strychnine and 13 of them died, making only 4.1 per cent. mortality. In animal experimentation the injection of small amounts of strychnine, morphia, nicotine and curare

not only had no preventive action, but made the results worse than the control. Alcohol, coffee, and tea, seem to be of some use when used in adequate quantities. It is often said that alcohol, when taken in quantities sufficient to cause profound intoxication, will avert or weaken the paralytic symptoms. But such an excessive use of alcohol must be avoided, as it is proved in animal experimentation that this exerts a decidedly unfavorable effect.

Artificial respiration even for one hour must be tried, and an intravenous injection of saline solution impregnated with oxygen is also recommended.

Specific Treatment.—Sewall found that the pigeon can be gradually rendered resistant to increasing doses of *Crotalus* venom by injecting small sublethal doses repeatedly. He finally succeeded in bringing a pigeon to withstand ten times a fatal dose. Calmette, in his first work on venom immunity, showed that an animal inoculated with sublethal doses of heated solution of cobra venom attains a certain degree of immunity which enables it to resist a certain fatal dose of the venom. A similar result was obtained by Phisalix and Bertrand with viperine venom. Calmette pursued this subject further and could finally show that guinea-pigs and rabbits acquire an immunity against the venoms of cobra after repeated inoculations of small amounts of the same, and that not only against cobra, but also against certain quantities of the viperine or other venom. He found also that the serum of such immunized animals has the power to counteract the poisonous effects of venom in a second animal, if the serum has been inoculated into the latter previous to the injection of the venom.

According to Phisalix and Bertrand, who worked with viperine venom, an injection of 0.4 mg., heated to 75° C. for five minutes, into a guinea-pig will enable the latter to withstand the same amount of the unheated poison after two days. Fraser later confirmed Calmette's results, while Calmette carried on his immunization work still further and finally prepared an antivenomous serum, by immunizing large animals like horses and asses, which he used for human cases.

Calmette recommended, for the production of an antivenin for cobra venom, primary injections of small animals with venom mixed with 1 per cent. calcium chloride; after four injections of this modified venom, gradually increasing doses of pure venom are injected, always carefully watching the weight of the animal. He also recommends the modification of the venoms to be employed by heating to 75° C. for 30 minutes. The antivenin which is issued from his institute is obtained from horses immunized against about 2 grams of unmodified venom (1 m. l. d. for a horse is 0.01 of cobra venom).

The immune serum is collected under ordinary aseptic precautions, and placed in small bottles holding 10 Cc., which are then heated to 58° C. for one hour. According to Calmette such a serum will keep for two years. A fluid antivenin may undergo certain external changes (flocculent precipitate) after being kept for some time, but its antivenomous power remains generally unaffected. Such precipitate must be removed by filtration through sterile filter papers, before use. Dried antivenin in sealed tubes will last for an indefinite period; before using, it is dissolved in sterile water. Calmette considers that an antivenin, of which 2 Cc. will

neutralize 1 mg. of cobra venom mixed *in vitro*, is sufficiently strong for practical purposes, and the injection of 20 Cc. of this antivenin is recommended by him in case of snake bite; in other words, an amount sufficient to neutralize 10 mg. of cobra venom.

The amount of venom injected by a cobra at one bite is estimated by Lamb to be 0.231, Cunningham 0.256, and Rogers 0.249 gm. If we accept these figures there would still be over 200 mg. of unneutralized venom, after the injection of 20 Cc. of antivenin. The minimal lethal dose of cobra venom for a man of 120 to 140 pounds is estimated to be 0.01 gm. (Calmette), 0.031 (Fraser), 0.015 to 0.0175 gm. (Lamb). Fraser who once prepared a fairly active antivenin, finally expressed his belief that more than 350 Cc. of the antivenin, injected intravenously, would be necessary to save a man from the effects of the bite of a cobra. Both the mode of administration of the antivenin and the length of time elapsing since the injection of the poison make the therapeutic value of the antiserum very different.

If the antivenin is injected directly into the vein its action will be much quicker than when it is given subcutaneously. The longer the delay of the injection of the antivenin, the greater is the amount of the serum required, until a point is reached when the antivenin will no longer save the animal. In a series of therapeutic experiments Noguchi has proved that the affinity between venoms and antivenins is very great, and the use of an antivenin in human cases has a most encouraging prospect.

A further question of great importance is that of the specificity of an antivenin. C. J. Martin first pointed out that the antivenin prepared by Calmette, by injecting cobra venom, had almost no protective property against the venoms of the Australian snakes. Lamb's later systematic investigations on this particular point have led him to believe that an antivenin prepared by injecting a particular poison is antitoxic only for the venom used for the immunization, and has almost no action upon other venoms. Kanthack was also convinced that the action of an antivenin is limited to the venom employed for its production. Noguchi has found that the action of an antivenin is highly, if not absolutely, specific both *in vitro* and *in vivo*. It is of great interest and importance that the hæmolytic and neurotoxic principles of different venoms are not identical in regard to their behaviors toward the anti-bodies; in other words, the anti-hæmolytic or the antineurotoxic constituents of a given antivenin will neutralize respectively the hæmolytic or the neurotoxic principles of the venom employed for its production, but has no, or very slight, action upon the same named principles of alien venoms.

Antivenins for cobra, daboia, Bungarus, Crotalus, water moccasin, Hoplocephalus curtus, and Trimeresurus, have been prepared by different workers, but their antitoxic value has never been high, as compared with that of diphtheria antitoxin. An antivenin for the cobra lecithid, or for the cobra venom from which the lecithid is removed, can readily be produced in animals, and their action is specific.

A polyvalent antivenin,—one prepared by treating animals with several venoms,—might prove of practical value, but little work has been done on this line. Calmette's antivenin is prepared by a mixture of several venoms in different proportions, still the amounts of other venoms than that of

cobra are so small that the result is that his antivenin is only of some value against the action of cobra venom.

The therapeutic value of antivenin depends upon the possibility of preparing an antivenin of greater potency than hitherto has been accomplished, and when such an object is reached our specific treatment of snake bite will be perfect. For the present, beside the use of a specific antivenin, the local treatment with any of the above mentioned substances, combined with a general stimulant, such as tea, coffee, or alcohol, is indispensable.

CHAPTER XIII.

AUTO-INTOXICATIONS.

By ALONZO ENGLEBERT TAYLOR, M. D.

UNDER the term intoxication we understand a state of perversion of physiological function induced by the presence in the body of abnormal substances or by an excess or deficiency of normal metabolic constituents. Under the term *constituent* is understood not only materials of nutrition and metabolism, but also the physiological fluids and secretions associated with the different functions. It has been long apparent that the pharmacological definitions of intoxication are too narrow to comprehend the acts of morbid physiology; a definition from the point of view of general and experimental pathology must be made as broad as here stated. The mere presence of a known poisonous agent, the presence of an excess, or the absence of the adequate amount of a normal substance, need not lead to any intoxication demonstrable under the circumstances of the occurrence or experiment; the reason for this lies in the singular adaptability of the metabolism and in the enormous toleration of the organism. To establish an intoxication there must be some disturbance in the function of the body. The definition must not be made so rigid as to exclude the morphological results of nutritional and metabolic abnormalities. We cannot afford to exclude from their bearings on intoxications the inflammations and degeneration produced in morphological structures by poisons, even at the risk of an apparently absurdly broad expansion of the term intoxication. A close consideration of the modes of action of poisons will justify this standpoint.

A general classification of endogenous intoxications, useful solely as a working scheme, is contained on page 267. It is apparent that the point of view is not consistently maintained, in that the classification is in part based on the chemical etiology and in part upon the function or organ involved.

Under auto-intoxications we group the intoxications of endogenous metabolic order. The endogenous parasitic intoxications exhibit relations that are often very intimate. Indeed, it may be assumed that in the majority of infectious diseases a part of the deleterious result is due to auto-intoxications secondary to the metabolism of the bacteria, but these have necessarily no relations to the specific poison of the particular microorganism. Since in some instances no other intoxications are induced, we may infer that some microorganisms are harmful solely through the excitation of an auto-intoxication. These auto-intoxications are of the nature of accelerations and exaggerations of normal processes—catabolism, oxidation, and cytolysis.

Exaggerations of catabolism and oxidation are common in the infectious diseases. Individuals with infections are not upon a metabolic

balance; when no food is taken, the output is greater than a starvation output; and it often exceeds the input by more than a starvation output when the digestion is sufficient to maintain an ordinary balance. This exaggerated catabolism may affect both the carbohydrate and nitrogenous metabolism. The patient wastes, owing to the excessive combustion of fat and muscle, and the end-products of the excessive protein metabolism are found in the urine.

Endogenous Intoxications.	Parasitic.	{ Alimentary. Systemic.	The	{ Due to bacterial processes.	
				{ Due to higher parasites, as vermes	
		{ Oxidation. Distoxication. Overexertion.	{ Suboxidation. Superoxidation. Insufficiency of oxygen.		
		{ Retention intoxications	{ Retention of bile. Retention of perspiration. Retention of carbon dioxide. Retention of fæces. Suppression of urine.		
	Metabolic.	Salts, acids, alkalies; acidosis.			
		Fever.			
		Infections.			
		Neoplasms.			
		{ Metabolism of protein.	{ Cystinuria. Alkaptonuria. Uræmia.		
		Metabolism of nuclein. Gout Oxaluria.			
		{ Metabolism of carbohydrate	{ Glycosuria. Diabetes.		
		Metabolism of fats. Acetone complex.			
	{ Diseases of special or- gans.	{ Thyroid, adrenal, pituitary bodies. Pancreas, liver, etc.			

An *acceleration of cytolysis* is commonly observed in infectious diseases. An excellent illustration is afforded by the red corpuscles. The life of the erythrocyte is limited. There is a regulatory mechanism whereby the formation of new cells is proportioned to the destruction of circulating cells; and there is a great reserve power of compensatory over-production. A prolonged excessive destruction of red corpuscles, however, usually overtakes the centres of regeneration, and a reduction of the unit of circulating cells is the result. An acceleration of the normal rate of destruction of erythrocytes is a very common result of infectious diseases. It is usually not to be attributed to the specific poison. Some of the poisons, as the venoms, are directly erythrolytic and certain bacteria contain similarly active substances; but of the known and isolated toxins, few are erythrolytic, and the erythrolysis must be attributed to other than the principal product of the bacterial metabolism. In nephritis, carcinomatous cachexia, scarlatina, and in toluylene-diamine poisoning, for example, we have the same oligocythæmia, resting, according to our present knowledge, upon an acceleration of the normal rate of destruction of red corpuscles. Similar considerations hold for the glandular structures of the body, especially the liver and kidney. A certain number of liver cells are constantly passing through degeneration into death, being replaced by new units derived from healthy cells. If the number

of cells dying be enormously multiplied in the unit of time, the organ will exhibit a notable degree of degeneration unless the production of new cells keeps pace with the increased destruction. Should the exaggeration of cell destruction be very extensive, reproduction could not keep pace, for the simple reason that the greater the cytolysis, the fewer the number of cells upon which the reproduction as well as the functions must devolve. Such cytolytic degenerations are most common in infectious diseases. How these accelerations of cytolyses are brought about we do not know. The nearest suggestion is that the process is one allied to fermentation, and this is supported by chemical study and by the observation that autolysis is more rapid in diseased and degenerating than in healthy organs. Another suggestion is that there is a chemical combination between some poison and a protoplasmic or nuclear constituent, resulting in the death of the cell. This has been made positive for certain cells by recent researches in experimental cytolysis, but we do not know to what extent it occurs in natural disease. Lastly, it might be held to be the result of excessive function, the death of cells being proportional to their overwork. This might hold in some of the acute infections with very excessive catabolism, but it could scarcely account for extreme degrees of degeneration in cases of chronic course with little demonstrable excessive catabolism.

However produced, it is apparent that the functions of tissues must be disturbed by these cytolyses and an auto-intoxication might result. To what extent this appears in clinical symptomatology and in the course of these diseases, we can only conjecture. It is possible that the products of tissue degeneration may be in themselves toxic. Thus cholin is derived from the cleavage of lecithin, and recent investigations have suggested that possibly to this or allied substances may be attributed some of the symptoms observed in general paralysis and other degenerative diseases of the central nervous system. In tetanus, the specific toxin seems almost entirely to dominate the symptomatology and these additional processes are not observed; tetanus is almost as specific and localized an intoxication as strychnine poisoning. In sepsis, on the other hand, the exaggeration of catabolism and cytolysis is so marked as to suggest that in these directions lies the chief and specific intoxication. This is not the place for a discussion of the nature of the infectious processes, but, in connection with true metabolic auto-intoxications, these secondary auto-intoxications associated with infectious diseases demand a brief mention.

To Bouchard belongs the credit of having first systematically considered the auto-intoxications from the general point of view of metabolism. During recent years an enormous amount of work has been directed to the problems of auto-intoxication and diseases of metabolism. Withal, our knowledge of auto-intoxications and of the pathology of metabolism is in its earliest infancy. In no intoxication do we possess such direct knowledge as we have concerning a large number of chemical poisons. For this the extreme complexity of the relations is responsible. Nor can much be expected until general and chemical physiology rest upon a broader basis. Once the actually toxic substance in an auto-intoxication is determined, the properties of that substance become a purely pharmacological question. But before the pharmacological investigation of such a sub-

stance can hope to elucidate the relations that are sure to be all-important in the delineation of an auto-intoxication, this pharmacological investigation must enter upon fields to which it is now almost a stranger. Such fields are: The relation of chemical composition, constitution, and configuration to the reacting organism; the reaction between protoplasm and poison; the velocity of toxic action; the nature of toleration and immunity; the interreaction of poisons upon the chemical reactions of metabolism; and the relations of solubility, co-efficient of distribution, ionization, and velocity of diffusion to toxic action. Prerequisite to such investigation, the future development of physiology and pathology will need to elucidate the relations in metabolism of four general factors: The role of fermentations, the validity of the law of mass action, the properties of colloids, and the relations of electrolytes to the colloids.

A separation of auto-intoxication from the general pathology of metabolism is not possible, since all alterations in general metabolism, if they lead to consequences, thereby become auto-intoxications. It is furthermore desirable from every point of view that the study of the auto-intoxications should be carried out from the point of view of and based upon the physiology of metabolism. We are all familiar with the conception of the chemistry of life as a series of processes building up to the cells and dismantling from them, assimilation up to the plane of biological dignity and dissimilation to the plane of simple products. The possibility of a misstep in the various stages of anabolism or catabolism would furnish the occasion for a perversion of function, an intoxication. It is upon these general considerations that the current views of auto-intoxication are based. The preaching of Bouchard is to the effect that the body is constantly on the verge of an intoxication, particularly through a perversion of the catabolic processes, though qualitative variations in anabolism could produce the same result. The danger of this conception is that it disregards entirely two most prominent attributes,—the power of adaptation to alteration in the media of existence and the power of compensation, of carrying an overload. We have many illustrations of the depletion and overtaxation of certain organs and functions and of how admirably the body compensates for them. For every function, it is known that a heavy overload may be well borne through a prolonged period. Under these circumstances it is absurd to say that we are all on the verge of an auto-intoxication, living, so to speak, over a charge of dynamite that may each instant be provoked to explosion. This view of auto-intoxication is an unwarranted use of a physiological concept. The animal metabolism cannot be compared to a light see-saw board, balanced upon a knife-edge, tipping at the slightest weight; but rather to a heavy see-saw board, balanced upon a broad timber, and too rigid to tip except upon the superimposition of a notable weight. This conception of our metabolism and its leeway of adaptation and compensation, is not only supported by our best chemical studies upon the subject but is in harmony with the common-sense experience of mankind. And it is to the use of this loose and subjective interpretation of the facts of metabolism and their relations to disease, that the term *auto-intoxication* has become the limbo into which untrained practitioners now consign their undiagnosed cases.

GASTRO-INTESTINAL AUTO-INTOXICATION.

In no subject in medicine is there today more confusion than in gastro-intestinal auto-intoxication. This must in the first instance be separated from exogenous intoxication. This is difficult, particularly with respect to intoxication from decomposed food. It is to be distinguished from the gastro-intestinal infections. For these we assume that they cause disease in the same manner as systemic infections, by the elaboration of specific toxic substances. That the gastro-intestinal as well as the systemic infections do entrain real auto-intoxications by disturbing the natural progression of metabolism, cannot be doubted. Lastly, gastro-intestinal auto-intoxication ought to be separated from indigestion, dyspepsia, gastritis, and enteritis. For these diseases, still more than for the specific infections, is it certain that auto-intoxications constitute a fraction of the morbid consequences. The question that the future must determine concerns the magnitudes of the different factors. Our *present* knowledge of the diseases of the alimentary tract indicates that auto-intoxication in the strict sense plays a subsidiary rôle. Future investigations may demonstrate the contrary.

A discussion of gastro-intestinal auto-intoxication in the strict sense may, according to our present knowledge, be divided into five headings: Digestive fluids and secretions; normal products of digestion; abnormal products of digestion; substances formed normally from food by bacteria within the alimentary tract; and abnormal products of bacterial disintegration.

Intoxication by Resorption of the Digestive Juices.—The digestive juices have a certain toxicity independent of their salts and reaction. Pepsin, trypsin, and erepsin, when injected into the circulation, produce cellular degenerations, alterations in the corpuscles and coagulability of the blood. It is by some assumed that these ferments are resorbed in normal life and rendered harmless by some process of distoxication. This granted, it is natural to assume next that the postulated distoxication may become disturbed and an auto-intoxication result. For the assumption that the ferments are resorbed, there is no foundation beyond the fact that the tissues and circulating fluids of the body contain normally traces of proteolytic, lipolytic, and glycolytic ferments. If these are to be regarded as derived from the digestive glands, it is more natural to assume that they have passed into the circulation directly than to assume a secondary resorption from the lumen of the tract. That the intestinal tissue behind the lining epithelium contains ferments is an experimentally established fact. Beyond this there is not a single reported experimental fact, exact observation, or clinical fact, that is explained by the assumption of the resorption and non-distoxication of the digestive juices. There are good reasons to question the resorption of ferments. Ferments are colloids, and, as such, unadapted to absorption. The pepsin and curdling ferment are digested by the trypsin; the salivary ferments are digested by the pepsin; and, according to our present experimental knowledge of the constitution of ferments and their hydrolysis, the products are amido-acids. These ferments, with those of the pancreas and succus entericus, are exposed to putrefaction by bacteria, to which they are very sensitive. Ferments are prone to hydrolysis, a fact capable of ready test-tube demonstration

The Products of Normal Digestion.—Some of these are toxic. The albumoses and peptones, when injected hypodermically, produce fever, leukocytosis, alterations in the coagulability of the blood, hæmolysis, and cellular degenerations of mild degree,—all conditions not particularly associated with so-called gastro-intestinal auto-intoxication. In the severe degenerative diseases, as acute yellow atrophy of the liver, acute pancreatitis and septic exudations, these proteins may be found in the blood plasma; there is, indeed, a probability that albumosæmia regularly accompanies fever. The writer is acquainted with no experimental work or clinical investigations tending to show that these lower proteins are responsible for any gastro-intestinal auto-intoxication.

The amido-acids are quite innocuous so far as they have been investigated and in the quantities that could be met with. Amido-nitrogen is found in all organs and in the circulation. In conditions attended with excesses of cellular degeneration, as in acute yellow atrophy of the liver, large quantities of these substances have been found in the blood and the tissues. There are no reported analyses tending to show that, in connection with gastro-intestinal auto-intoxications, the content of amido-nitrogen in the blood or urine is increased.

Charrin has attempted under the term "fever of digestion" to set up, as a clinical entity in children, a condition assumed to be the result of an abnormal performance of the digestive functions, unassociated with any infection. The descriptions lack clearness and precision, and these defects have been exaggerated by the later reports.

The products of the digestion of fats must also be held guiltless. Glycerine is somewhat toxic; there is normally no glycerine in the urine. Since the fats are found resynthesized in the retroperitoneal lymph vessels, it is apparent that the glycerine split off during the digestion has been again used in the recombination. The fatty acids themselves cannot be a factor, because, when administered, they are easily absorbed and converted into fats by the addition of glycerine. The products of the carbohydrate digestion are entirely innocuous.

Abnormal Products of Digestion.—Of qualitative variations in the digestion of protein we know little. In the complete hydrolysis of protein a large number of amido-acids are formed. Recent investigations indicate that the different proteins contain the same amido-acids but in different relative amounts and probably in different combinations within the molecule. In the act of absorption, the products of the protein digestion are reconverted into protein, not into the original forms present in the diet, but into serum albumin and serum globulins. In the act of absorption further, the biological stamp is placed upon these proteins, in particular upon the globulins. Whatever of these processes of synthesis is not completed in the intestinal mucosa is completed in the liver. It is conceivable that under abnormal conditions the products of digestion might suffer some alteration, either within the tract or during the process of absorption. We have no facts that indicate that such is the case. There is, in connection with the digestion of fats, one recognized possibility for an abnormal deviation,—the formation of β -oxybutyric and diacetic acid. As will be described under acidosis, there is one group of cases of acetonuria associated with gastro-intestinal symptoms which may be of gastro-intestinal origin, though at present the

evidence is against this direct relationship. In connection with the digestion of carbohydrate, it must be borne in mind that a gastro-intestinal oxaluria is theoretically possible, the oxalic acid being derived from glucose. Cystinuria and alkaptonuria were once regarded as of gastro-intestinal origin, but this point of view cannot now be maintained.

Substances Formed by Bacteria from Normal Food Within the Alimentary Tract.—The normal digestive tract contains many saprophytes and not a few pathogenic bacteria. The temperature is favorable, nutrient media are abundant, the products of their metabolism are regularly removed, and we have the best evidence that fermentations and putrefactions are constantly in operation. The material consumed in these operations is not large; over nine-tenths of the food is absorbed in digestion and the larger portion of the remainder is residual in the faeces. This is not due to the antiseptic properties of the digestive juices (which are not pronounced), but rather to the rapidity of the processes of digestion and absorption, and to the brief residence of the residue in the tract.

Do the products of the normal bacterial disintegration of normal food give rise to intoxications? Under conditions of increased virulency upon the part of the bacteria normally present, may not greater quantities of the normal products be generated, with the causation of an intoxication? One must attempt to separate systemic intoxication from local irritation. The stools of children with acute enterocolitis may present the acidity of a tenth-normal acid, due to acetic and butyric acids. Now since the ammonia and fixed alkalies of the urine need not be increased in these cases, it is clear that the children are not suffering from an acid intoxication by absorption. But there can be no doubt that such a degree of acidity causes irritation and inflammation of the mucous membrane and might be responsible for colic, diarrhoea, and fever. The products of normal fermentation and putrefaction within the alimentary tract are, so far as we know, the following: From the fermentation of carbohydrates are derived formic, acetic, butyric, propionic, valerianic, lactic, succinic, and traces of oxalic acids. Apart from oxalic acid, none of these are toxic beyond their acidity. The quantities formed are not large. They are in large part absorbed, since normal faeces contain but traces of them. Their neutralization and oxidation entrains, in all probability, no metabolic difficulties, and we may regard them as innocuous. The same acids could in part, together with oxy-acids, be derived from the bacterial disintegration of the fats; this occurs but to a slight extent, since fatty acids are very difficult of fermentation. The putrefaction of protein yields the derivatives of the benzol nucleus—indol, skatol, phenol, and cresol; amido-acids, such as leucin, tyrosin, asparaginic and glutamic acids; hexone bases and their derivatives; sulphurous bodies, such as mercaptan, hydrogen disulphide, and other unclassified bodies containing neutral sulphur. Indol, skatol, phenol, and cresol, are, in the quantities concerned, quite non-toxic. The amido-acids are quite harmless; they are absorbed and either elaborated or oxidized. The sulphur bodies are of unknown importance. Hydrogen disulphide is of course toxic, but the quantities concerned are trivial. Carbon dioxide, nitrogen, acetone, alcohol, methane, and other hydrocarbon gases that exist in traces, can not be convicted of any toxic effects.

Thus the sum total of our present knowledge is that in the normal bacterial disintegration of foodstuffs in the alimentary tract no known toxic substance is formed. To plead that since some of the denominated substances are toxic in overwhelming doses, they must be therefore in every dose poisonous to some degree, and that consequently we are all constantly intoxicated to a slight extent but are able to nullify the effects, is not a proper toxicological argument. This is indeed the position of the Bouchard school, well exemplified in the expression "Auto-intoxication à l'état normal." This theory is lacking in objectivity and in its concrete interpretation incapable of control. A normal life cannot be termed an auto-intoxication if this term is to retain any meaning.

Are these bacterial processes sometimes so excessive as to cause a direct intoxication? In infantile enterocolitis the organic acids may be produced in excessive quantities and possibly these are responsible for some of the acid intoxications; we do not know whether these fatty acids cause acidosis or whether it is always due to the acids of the acetone group. Intoxication with hydrogen disulphide occurs certainly, though rarely. When so much hydrogen disulphide is absorbed as to appear unoxidized in the urine, it is proper to attribute to it the suggestive toxic symptoms that are present. Large quantities of lactic acid are sometimes found in the stomach; indeed, there are paroxysmal attacks accompanied by excessive formation of this acid. There is no evidence that it is absorbed, since the lactic acid met with in the urine is optically active, while that obtained from the stomach is inactive.

In many conditions of the alimentary tract the benzol derivatives are increased in the urine. While this should be interpreted to mean nothing more than that the bacterial processes in the intestine are increased, it is usually interpreted as a sign of auto-intoxication. If the pancreatic duct be ligated, the conjugated sulphates will sink to almost nothing; the bacteria act not on the protein but most energetically upon the products of pancreatic digestion. Indol and skatol are products of the action of bacteria on tryptophane, an end-product of tryptic digestion. They are for the most part absorbed, eliminated paired with sulphuric and to some extent with glycuronic acid, and in small part as oxyacids. Skatol-carboxylic acid is in part eliminated as a salt, in part oxidized. The phenol and cresol are derived from tyrosin. They are absorbed, in large part oxidized to hydrochinon and pyrocatechin (which pair with sulphuric acid); the rest is eliminated paired with sulphuric and glycuronic acid. Paraoxyphenyl-acetic and -propionic acids, intermediary products in the derivation of phenol from tyrosin, appear as salts in the urine, but bear no constant relation to either the tyrosin or the phenol. Hippuric acid, apart from that obtained from the vegetable diet, is probably derived from phenyl-alanine. Normally the absorption of these substances is very good, but that cannot be assumed and should be controlled by examination of the stools. The conjugation of the aromatic bodies occurs largely in the liver, to some extent in the lungs and kidneys; the oxidations occur in large part in the liver.

There is normally little putrefaction but much fermentation in the small intestine. Obstruction of the colon leads to little increase in putrefaction, obstruction of the small intestine leads to a morbid increase; nevertheless in a few reported cases there was no increase in the urinary

aromatic sulphates. Diarrhœa usually leads to a diminution of putrefaction, but in typhoid fever, dysentery, and intestinal tuberculosis, we often observe an increase. There is no relation between gastric acidity and intestinal putrefaction; the hydrochloric acid is too distant from the colon. There is no constant relation between intestinal putrefaction and the biliary secretion; there is an antiseptic tendency in the bile, but it is not pronounced. Intestinal putrefaction is dependent to some extent upon the diet. With an excess of protein, an abundant substrate is afforded the bacteria. In the qualitative sense the products of intestinal putrefaction will depend to some extent upon the particular proteins contained in the diet. Proteins that yield much tryptophane on hydrolysis will yield much indol, skatol and their derivatives; proteins that yield much tyrosin on hydrolysis will yield much phenol and cresol and their derivatives. Thus serum albumin and globulin, fibrin, casein and histone yield large amounts of tyrosin and but little tryptophane, while gelatine, elastine and egg-albumin yield much tryptophane.

Intestinal putrefaction is dependent on the diet apart from protein. The ingestion of carbohydrate tends to reduce the putrefactive processes, presumably by virtue of the acids of fermentation. In starvation the putrefaction is low. The flora of the alimentary tract is of great importance, though as yet little studied in detail. Certain of the actively putrefying anaërobic bacteria produce no indol or skatol but much phenol; the colon bacillus is an active producer of indol. Variations in the flora may be of determining influence in the quantitative relations of the different aromatic substances.

There is no constant relation between the protein ration and the output of aromatic substances. No one single aromatic substance bears a constant relation to the total conjugated sulphates; this is to be emphasized for indican. One cannot judge of the total paired sulphates from the indican; one may see high indicanuria with a low total, or high values for the total with but traces of indican. There is no constant relation between the aromatic substances and the bacterial count of the fæces. The least faulty method of determining the extent of intestinal putrefaction is by the estimation of the conjugated sulphates. Nevertheless this may yield a totally false interpretation. One sees individuals in perfect health who eliminate large quantities of aromatic substances.

What is then the exact meaning of an increase in benzol derivatives in the urine? A normal output need not indicate a normal state of intestinal putrefaction; an excessive output indicates that more protein than usual is undergoing putrefaction in the alimentary tract. (We are not here concerned with tissue putrefaction, which of course gives rise to an excess of aromatic bodies in the urine.) This may be due simply to some individual idiosyncrasy, to peculiarities in the diet, to a heightened virulence of the bacterial flora, to the presence of a particular bacterium, or to the retention of the food in the tract. Does it necessarily indicate an intoxication? By no means. A certain amount of intestinal putrefaction is normal; an increase may be entirely innocuous. A constant relation between putrefaction and intoxication could hold only if the aromatic bodies were in themselves toxic, if the process of oxidation and pairing were deleterious to the body, or if the formation of the aromatic substances bore a constant relation to the elaboration of some

unknown poison and to the symptoms. There is no evidence that the substances are themselves toxic to any degree, or that the conjugation places any burden upon the body. The amount of sulphuric acid available for conjugation with the aromatic bodies is limited by the extent of protein catabolism; and the actual availability of it will be determined, in part at least, by the excess of cations in the diet. It is possible that the conjugation with glycuronic acid may be in part reciprocal to the conjugation with sulphuric acid. We have no method of estimating the quantity of aromatic bodies that are eliminated with glycuronic acid. We have no feasible method of estimating the oxidized aromatic substances. There is no clinical parallelism between symptoms and conjugated sulphates in the urine, either in degree or in the onset and disappearance. What is all along actually assumed is that other substances, poisons, are produced by the putrefaction; and as the degree of putrefaction may be often approximately measured by the aromatic substances, the degree of the hypothetical poisoning is also so measured.

TABLE OF AROMATIC URINARY PRODUCTS OF INTESTINAL PUTREFACTION.

Tryptophane	→ Skatol-acetic acid →	— Indol →	{ Indican. + Indoxyl-glycuronic acid. Oxidation products.
		— Skatol →	{ Skatol-sulphuric acid. + Skatol-glycuronic acid. Oxidation products. Skatol-carboxylic acid.
Tyrosin.	{ p-Oxy-phenyl-acetic acid →	{ As salt. With sulphuric acid.	{ Phenol-sulphuric acid. + Phenol-glycuronic acid. Hydrochinon-sulphuric acid. + Pyrocatechin-sulphuric acid. + Benzoic acid → Hippuric acid.
	{ p-Oxy-phenyl-propionic acid →	→ Cresol →	
		As salt. With sulphuric acid. + Benzoic acid → Hippuric acid.	
Phenyl-alanine	→ x → x →		

The crosses indicate the substances that are included in the method for the total ætherial sulphates. Since we are not able at the present time to estimate or control the amounts of aromatic derivatives eliminated in other form than paired with sulphuric acid, it is obvious, not only that the estimation of indican must often be of no value, but also that the estimation of the conjugated sulphates must often yield an uninterpretable result, and one that will permit of no inference as to the degree of intestinal putrefaction.

Abnormal Products.—When proteins are subjected to putrefaction, a large number of alkaloid-like substances are formed, commonly termed ptomains. They include a large number of substances of the fatty series, amines, and members of the pyridin and the chinolin series. In addition there are a number of bases, some belonging to the pyridin group, others yielding reactions of chinolin, while still others resemble muscarin. Most of these ptomains are innocuous. None of them except

the simple amines have ever been found in the urine or faeces of normal individuals or of those suffering from any diseases except cholera, idiopathic cystinuria (occasionally dysentery, enteritis, and obstruction), and true ptomain poisoning due to the ingestion of decomposed protein. Several years ago the writer made a systematic search for ptomains in the urine and faeces of patients with pernicious anæmia, gastric carcinoma, chronic gastro-intestinal disease, and subacute partial obstruction of the intestine, always with negative results. It is known from experimental work that time is required for the elaboration of ptomains, particularly the toxic ones; in general no poisonous bases are formed in less than ten days. That these relations are, however, only relative is shown by the fact that in some of the well-studied cases of ptomain poisoning due to the ingestion of decomposed food, the analytically incriminated foods have been but a few days old. We possess no information that in the so-called gastro-intestinal auto-intoxications (the ingestion of decomposed foods must be excluded) ptomains have ever been found. Since a certain decomposition of food occurs within the alimentary tract and the degree of this decomposition may be increased under certain conditions, we are driven to the conclusion (*a*) that there is not time for these changes to proceed to the stage of ptomain formation, (*b*) the ptomains are decomposed in the system, or (*c*) the decomposition of protein in the intestine is different from that outside the body. The last conjecture may be dismissed. We are left to choose between the other possibilities: Either ptomains are not formed in the alimentary tract (apart from the known instances already mentioned) or they are formed and dioxicated. What evidence is there that ptomains are dioxicated? In experimental work, ptomains are eliminated in the urine just as in idiopathic cystinuria. The general consensus of opinion is that for the diagnosis of ptomain poisoning, the presence of the poison must be demonstrated. Such chemical demonstration has never been accomplished for the class of cases under discussion. Of experimental demonstration, we have largely the measurement of the urotoxic co-efficient. But since the normal urotoxic co-efficient is valueless, deviations are of little import. The strict conclusion to be drawn from our present knowledge is that the term "ptomain poisoning" should be confined to instances of intoxication due to the ingestion of decomposed food and accompanied by the elimination of the poison, and to instances of decomposition within the tract in which toxic ptomains may be isolated. All other usage is guess-work. The presence of cadaverin and putrescin would mean little, for, apart from their harmless roles in cystinuria, they are to be found in old digestion experiments, where they are derived by fermentation of lysin and ornithin, and thus they do not necessarily indicate an abnormal bacterial decomposition. The neurine group has been considered responsible for some of the symptoms of Addison's disease, though without chemical demonstration.

There are several clinical symptom-complexes in which, though the term ptomain poisoning is improper, there are reasons of fact and analogy that furnish some warrant for the use of the term gastro-intestinal auto-intoxication. What is needed in these domains is exact investigations,—accurate clinical observation and objective chemical research. While there is a large element of an art in practical medicine, diagnosis

ought to be an objective science. There is an element of fashion, personal or collective, in the manner in which the obscure conditions of disease are interpreted. The progress of the auto-intoxication propaganda, like that of every other uncontrolled movement in practical medicine, is like the development of gossip in common life: The first person suggests that it might be so, the second states that it is so. The serious aspect of the situation, which, if we may judge by the history of medicine, is ephemeral and in a sense self-corrective (a good illustration is afforded in the history of the diagnosis of malaria), lies in the fact that positive diagnosis, however fictitious, inhibits investigation.

Tetany.—Under tetany we understand the full complex, excluding the atypical instances of peripheral or carpopedal spasm. The tetanies associated with extirpation of the thyroid, intestinal parasites, pregnancy and lactation, acute infections, exogenous intoxications, rachitis, and the so-called epidemic or occupational variety, can have no dependence upon the digestive tract.

Typical tetany of the severe form occurring in adults in association with gastric dilatation is rare and very fatal. The dilated obstructed stomach furnishes a most favorable opportunity for the decomposition of food. To determine whether these processes have gone to the stage of the production of poisons, the gastric contents and urine have been investigated. Hyperchlorhydria cannot be incriminated. In a few instances uncharacterized substances have been obtained from the gastric contents (method of Brieger) that were somewhat toxic to rabbits; in other cases the substances were innocuous. From the urine in a few cases, substances have been isolated that gave group reactions of ptomains but were not toxic on intravenous injection into rabbits. Up to the present, therefore, a ptomain poisoning has not been demonstrated for tetany. Tetanic seizures are observed in dogs in whom the duodenum is cut across and the ends brought into external fistulæ, so that the gastric contents leave the body; the results might be explained by the assumption that there is in the gastric secretion some substance, a constituent necessary to the intermediary metabolism, that should return to the circulation by intestinal resorption.

The tetany of children, associated with gastro-intestinal symptoms and diseases, is often accompanied by acidosis, and an excess of ammonia and of aromatic bodies in the urine. The toxicity of properly prepared extracts from the urine or digestive contents has not been studied. The association with the acidosis is of slight moment, since this is very common in children in subnutrition.

The Alimentary Tract.—Commonly regarded as intoxications are certain gastro-intestinal attacks associated with cutaneous symptoms. The symptoms are pain, vomiting, often diarrhœa, fever, followed by a general erythema, urticaria, or possibly by other exanthemata. Desquamation may follow. The symptoms in many cases resemble closely intoxication with shell-fish in susceptible individuals, less closely the drug-exanthemata. These attacks tend to recur periodically. Recovery usually follows promptly after gastric lavage, irrigation of the colon, and free purgation. Ptomains have never been reported in the contents of the tract or urine. The writer is acquainted with one case in which a careful search was made with negative results.

Not infrequently instances of severe violent disturbances of the alimentary tract are observed that bear all the external marks of an auto-intoxication. Usually no adequate cause is to be determined, particularly no gross dietary indiscretion. The attacks consist of sudden vomiting, that may be uncontrollable, extreme pain, profuse diarrhoea in some cases, and in others spasms of the intestine, with meteorism, vertigo, vasomotor dilatation, shock, local spasms, even convulsions and coma. It does not seem possible to consider these as indigestions or infections. If it is possible to exclude exogenous intoxication, the assumption of a gastro-intestinal auto-intoxication is justified, even though a chemical investigation (which has apparently never been attempted) should fail to isolate any known poison. This reasoning does not hold for the marasmus of enterocolitis. One must here choose between a gastro-intestinal and a metabolic auto-intoxication, and there has been so little work done that a definite opinion is not now possible. The recurrent vomiting of children will be discussed under acetone acidosis.

In connection with subacute, complete, or partial obstruction of the stomach or intestine, symptoms suggesting gastro-intestinal auto-intoxication are usually noticed. There is fever, albuminuria, headache, insomnia, a marked increase in the aromatic substances in the urine, sometimes exanthematous rashes, possibly severe nervous symptoms, which subside when the obstruction is relieved. The difference in the appearance of patients with gastric carcinoma, before and after gastro-enterostomy, is usually so striking that one is driven to question whether this can be explained by the conditions of nutrition, and is not due in part to the removal of conditions of decomposition in the stomach. Nevertheless the definite demonstration is wanting. In not a few instances of chronic appendicitis, nervous symptoms have been prominent (even epileptic seizures), which disappeared with the removal of the appendix. Admitting the facts, the assumption of a gastro-intestinal auto-intoxication is hypothetical.

Constipation.—The diagnosis of auto-intoxication rests largely upon an excess of indican or conjugated sulphates in the urine. The elimination of indican and of the aromatic sulphates bears, however, no constant relation to the presence or absence of constipation; nor does the degree of increase in the aromatic substances in the urine bear any relation to the intensity of the symptoms. As previously stated, indicanuria is not a sign of auto-intoxication, nor does it afford any index of the elimination of other and toxic substances. The urine and feces of patients with constipation have been analyzed without success for ptomaines. An illustration of the fictitious value of the interpretation of the symptoms of constipation is afforded by the fact that they are at all times more pronounced in women than in men, and particularly marked during the menstrual period, which is, in all probability, to be explained as a mechanical result of the distension on the pelvic organs. It is also noteworthy that many of the symptoms of constipation are to be observed in association with abdominal and pelvic diseases unaccompanied by constipation. A recent suggestion is that the evil results of constipation may be due to the non-secretion, by the intestinal mucosa, of toxic substances, whose elimination is assumed to be a function of the intestine. For this hypothesis there is no evidence.

Nervous Dyspepsia.—This has been classed as a gastro-intestinal auto-intoxication. The absence of inflammatory lesions and abnormalities of

digestion, apart from variations in the secretion of hydrochloric acid, makes a conception of the etiology of nervous dyspepsia obscure but there is no good evidence that an auto-intoxication is present. It will not do to say that, since we know of nothing else, it must be an auto-intoxication; if we do not know of anything else and there is no exact evidence of an intoxication, we simply do not know the cause at all.

Nervous System.—For the etiology of a large number of diseases of the nervous system, (migraine, neuritis, epilepsy, myasthenia, melancholia, dementia paralytica, psychoses, and even periodic family paralysis) gastro-intestinal auto-intoxication has been invoked. The evidence comprises analogies between these diseases and conditions in the nervous system due to known poisons, the occurrence of constipation and often of an excessive elimination of aromatic substances, the occasional occurrence of acetonuria, the apparent relation of attacks to dietetic errors, the finding in nerve cells of lesions resembling those produced by experimental intoxications, and in the results of the measurement of the toxicity of the urine and, in some cases, of the perspiration. A perusal of the literature bearing upon the subject suggests that it is not the validity or natural probability of the findings above summarized that leads to the diagnosis, but rather a conviction of the insufficiency of the previously offered hypothesis. Of exact investigations there are none.

The Anæmias.—These have long been regarded as diseases of intoxication. The earlier theory of the gastro-intestinal origin of chlorosis is now generally recognized as disproved. For pernicious anæmia, however, a good case has been made out. The reasoning does not rest upon such indefinite facts as constipation or diarrhœa, indicanuria, acetonuria. That a persistent hæmolytic is at the bottom of pernicious anæmia is shown and this is one of our best studied effects of poisons, and, with the demonstration of the occurrence of a severe and persistent hæmolytic as the cardinal feature of the disease, a reasonable etiology is established. Earlier work made it probable that the poison was absorbed from the alimentary tract; this has been supported by the experiments with toluylene-diamine, and the analogy with the anchylostoma anæmia. It is supported by the histological findings, which indicate that the hæmolytic occurs in the portal system, and by the atrophy of the mucosa of the stomach and intestine, so often observed. Concerning the nature of the hæmolytic agent we know nothing. A ptomain it certainly is not. Years ago, the writer searched the fæces and urine of a series of cases systematically for ptomaines, with negative results. For leukæmia, we have no exact knowledge.

Asthma Dyspepticum.—Is there a dyspnœa of toxic gastro-intestinal origin? The experimental foundation for such a conception is to be found in the observation that in dogs with an Eck's fistula the ingestion of bouillon or meat is followed by acute dyspnœa. Children exhibit attacks of acute dyspnœa associated with alimentary disturbances and unaccompanied by any lesions in the thoracic organs or kidneys. The condition, not confined to children, has not been extensively studied. A close connection exists between the diet and exacerbations in the attacks. No poisons have been isolated.

Gastro-intestinal Albuminuria.—The kidneys are sensitive to poisons. In not a few instances of gastro-intestinal disturbances, albuminuria is observed, and it is common in poisoning by shell-fish and decomposed

foods. There can be no strong objection to this classification of the instances of albuminuria that occur in well-defined cases of gastro-intestinal diseases. But to go to the extent of the assumption, without exact evidence, that the so-called idiopathic, cyclic, and recurrent albuminuria rest upon an otherwise unmanifested gastro-intestinal auto-intoxication is surely unjustified.

ABNORMALITIES IN THE PROCESSES OF OXIDATION.

The relations of the existence, extent, and nature, of sub- and super-oxidation are intricate and, in part, undetermined. Upon a normal mixed diet, the body heat is largely maintained by the carbonous metabolism; on a protein diet, the protein metabolism will be so exaggerated as to supply the entire heat. The minimum is determined by the amount required to sustain the body temperature under proper conditions of control without food and at complete rest of voluntary movements. Since the body is sparse in its metabolism when deprived of food, the figures under these circumstances will be below the real normal; but it is the nearest approximation we can secure, since otherwise the heat of digestion introduces a factor of disturbance. For normal adults the minimum heat values may be given as 14 calories per lb. (30 cal. per kilo) per day. Elderly individuals may require less, children will require more, emaciated convalescents may maintain a balance upon as little as 10 cal. per lb. (22 cal. per kilo). The average is probably higher, and there are notable individual variations. Less than 10 per cent. of this heat is derived from the combustion of body protein utilized in the daily metabolism. To produce the rest, nearly 17 oz. (500 gm.) of sugar or 8 oz. (225 gm.) of fat are burned.

Under less experimental conditions of life than a fasting repose in a respiration chamber at constant temperature, these figures will be increased. On a usual diet, nearly twice as much protein would be dissimilated, so that a couple of hundred of calories a day would be there added. The heat dissipation will be somewhat increased under ordinary conditions. An increase in oxidation is observed following the ingestion of food, which is marked for protein, much less for carbohydrates and fats. This increase is not slight since the O-input and the CO₂-output after a meal may exceed the fasting figures by 30 per cent., and with forced protein feeding equal the entire fasting oxidation. The reasons for this fact, which has clinical bearings, are not entirely clear. Digestion is an exothermic process; but since the products must be reconverted, heat will be again absorbed. Peristalsis and the secretion of the digestive juices represent a certain slight heat production. The older idea, that this increase in oxidation represents an extravagance of luxury (in the sense that, like a spendthrift, the body increases its outlay with its income), has been shown not to hold good. The cleavage, after resorption of the protein, into the nitrogenous and the non-nitrogenous moieties, is held to account, in large part, for this increased oxidation. Apart from the obscurity of this explanation, it is not in harmony with the fact that the degree of this digestive increment of oxidation is apparently quite constant in percentage for a particular substance, and not dependent upon the quantity. This digestion-oxidation

is greater in the child than in the aged, low in the obese, and high in the convalescent.

Muscular exercise produces a great increase in the processes of oxidation. In the respiration experiment, this is limited to the movements of respiration, circulation, and peristalsis. The respiratory movements furnish a considerable percentage of the heat production. Ordinary work increases the oxidation processes by 50 per cent., heavy work may double the oxidation of the resting, fasting individual. Marked individual variations occur. Exercise of the untrained muscle increases oxidation more than in the trained muscle; exercise of the exhausted muscle especially is accompanied by superoxidation. The velocity of contractions in the unit of time increases the oxidation disproportionately. The weight of the individual is, for obvious reasons, of great influence. Lastly, there is the factor of temperament and facility. Two men of the same stature and weight will not do the same muscular task with the same expenditure of energy. This is not entirely a matter of training; some are, by nature and construction, economical of motion, others extravagant. Restlessness is a factor of influence. These considerations are of great importance; unless constant conditions can be secured, fair comparison between the sick and the well cannot be made.

Under the incidental oxidations are classed those associated with functions that have a *raison d'être* independent of the heat production, such as the protein and nuclein metabolisms. These are increased but slightly by exercise and to some extent by conditions in the diet. So long as the diet contains the normal quota of fat and carbohydrate, less than a sixth of the heat required for the body is derived from these incidental sources. There is a regulatory mechanism in the carbonous metabolism. When the other sources of heat are prominent the combustion of sugar and fat is reduced; that this is a limited adaptation is shown by the fact that the heat production, apart from the incidental combustions, is not reduced to *nil* when the individual is placed in an atmosphere of the temperature of the body, and by the continuation of sugar combustion when, to a mixed diet, protein is added in quantities sufficient to supply the body heat. Under these circumstances sugar is still burned and the needless heat dissipated by physical means. There is evidence that at higher temperatures, as in the Russian bath, the processes of oxidation in the body are actually increased. In considering the relations of oxidation in disease, we are concerned with the total alone; it is not necessary to state that a particular oxidation may be increased or decreased in health and disease.

Suboxidation.—Have we evidence of the existence of a state of general suboxidation? The metabolic heat production is derived from the movements of circulation, respiration and peristalsis, secretion, and the reactions of catabolism. The hypothesis of a retardation of metabolism means that these reactions would be accomplished with less consumption of material and production of heat than in the normal; and since the circulation and respiration act in part reciprocally to these, they would be reduced. The hypothesis of a retardation of metabolism means that the unit of protoplasm would have a lower level of metabolism. The unit of protoplasm in the cold-blooded animals has a very low level of metabolism, and in the hibernating animal a much lower level than during the summer. The hypothesis of a retardation of metabolism is therefore tantamount to

the predication that, as a diseased condition, the unit of human protoplasm can suffer a reduction in the plane of its metabolism. That this is true to a certain extent is illustrated by the economy in metabolism displayed in the chronically underfed. The real question is whether such a reduction as is assumed in the hypothetical retardation of metabolism is compatible with the relations of heat dissipation and body temperature. A moderate suboxidation could occur without reduction in the body temperature. There are four directions of heat dissipation: Radiation from the skin, evaporation of perspiration, respiration, and the heating of food and drink to the temperature of the body. The respiratory loss cannot be reduced below the values for the resting individual. The cutaneous radiation and perspiration are subject to a greater degree of regulation, and, with these physical regulations enforced to the maximum, the body temperature of the resting individual could be maintained upon less than the minimum values given. On how much less we do not know. Since, however, the body temperature is normal in individuals suspected of having suboxidation, the argument is concerned with just this rubric. A reduction of the body temperature would not in itself indicate suboxidation.

That such a state of suboxidation exists as an acute condition may be assumed, though no accurate studies of appropriate cases exist. In prolonged surgical anæsthesia and drug narcosis, following extreme hemorrhage, in shock, in asthenic infections, in terminal diabetic and cholæmic coma, such a condition probably exists. In these states the body temperature is low. This may be due in part to excessive heat dissipation, since many have extreme vasomotor dilatation. The renal functions are nearly abolished and analyses of the urine indicate a very low protein catabolism, far below that of starvation. The whole picture suggests prostration of all the vital functions, including that of systemic oxidation. The state is one adjacent to death and can be tolerated but a few hours.

In connection with chronic diseases, the use of the expression may be controlled by investigations, and, though these are very onerous, enough cases have been carefully studied to enable us to form a tentative judgment in the matter. Nowadays we read and hear much of suboxidation. It is particularly unfortunate to mix magnitudes of undetermined definition with purely fictitious terms. Suboxidation is the name of an objective condition, and subject to control as such.

There are four groups of chronic diseases in which suboxidation has been considered; obesity, the anæmias, myxœdema and cachexia strumipriva, and the cachexia of malignant diseases. The facts to be determined are: What is the condition of the nitrogenous and carbonous metabolism, how is the O-input and CO₂-output?

Obesity.—Is there suboxidation in obesity? Preliminary to this question a consideration of the relations of the sexual functions to metabolism is important. Castrated animals are more easily fattened than their normal fellows. In young animals this growth comprises a flesh- as well as a fat-mass. The question whether this rests upon a reduction in the oxidation processes is of great importance, because if it should be demonstrated that the plane of oxidation may be shifted by castration, the sexual glands would acquire a metabolic function allied to that of the thyroid. Castration in animals converts a nervous into a phlegmatic temperament, and we know as an experimental fact that the nervous

temperament is wasteful in movements, metabolism, and combustion. There is an actual loss of material attending the functions of the organs of reproduction, though we have no way of estimating it. The sum total of these influences is sufficient to account for changes of notable degree, though a measurement is impossible. In the end, therefore, the decision must be left to the metabolic experiment.

Years ago investigations were believed to have shown that the oxygen consumed by castrated animals was nearly 20 per cent. less than the amount consumed by the controlled animals. The methods were faulty, the experiments brief and the results excessive; such a degree of suboxidation would lead to the development of the highest degree of obesity within a very short time. Recently the work has been repeated with longer periods of observation; a positive evidence of suboxidation has not been obtained. Castrated dogs of both sexes (and unsexed women) exhibit the same carbonous and nitrogenous metabolism as the properly managed controls. In the current literature there is a general confusion of the indirect and the direct effects of castration on nutrition, metabolism, and combustion.

Coming to the question of obesity, there are two groups of fat people that present symptoms suggesting an abnormal metabolism: The excessively fat children, and those adults who leading active muscular lives, and, not being addicted to excesses in eating and drinking, become pathologically obese. There are two ways of investigating these cases: The method of metabolic and combustion experiment, and the method of prolonged observation on a known and controlled diet, with careful observation of the body weight. In the use of the method of metabolic experimentation, one must realize that much lower values will be secured than in thin individuals, without affording any basis for induction. The unit of substance necessary for a body is related only to the mass of the metabolic tissues. The bones, apart from the marrow, are practically of no metabolic moment; but, since they remain constant with respect to obesity, need not be considered. Little energy is required for fatty tissue. When an individual weighing 160 lbs. (70 kilos), in good nutrition, adds fat up to 220 lbs. (100 kilos), his metabolic transformations will not increase in the ratio of 16 to 22; the stout man will have about the same metabolism that he had when thin, and the unit of calories of O-input and CO₂-output per kilo weight will have decreased. To be of positive value the variations must exceed these relations. There have been some twenty investigations of the combustion-metabolism of cases of obesity. The results of these have been negative,—no evidence has been obtained that there is any reduction in the processes of oxidation. The error in the method of prolonged observation is the difficulty of determining the relations of water to solids, and of excluding dropsy. There are a few reported cases in which obese subjects have maintained their weight on a diet of very low caloric value (as low as 1,000 cal.). It is unfortunate that such an individual has not been placed on a respiration experiment. Investigations therefore tend to show that no such thing as suboxidation occurs in obesity.

Myxœdema and Cachexia Strumipriva.—The evidence bearing upon suboxidation in these diseases may be grouped under four headings: (a) The direct combustion experiment. In one case of sporadic cretinism the values, though low, were within the normal. (b) The clinical symptoms.

These suggest suboxidation. The patients incline to low body temperature despite the fact that, on account of the almost complete abolition of perspiration, the heat dissipation seems below the normal. These facts, while suggestive, do not directly indicate the existence of suboxidation; they indicate that the subjects have lost in part the power of suddenly increasing their combustion to meet the demands imposed upon it. (c) The results of thyroid medication. These are striking, but they bear only in part upon this question. The administration of thyroid preparations in the healthy, and to a greater extent in the myxœdematous, results in a marked increase in the protein catabolism and to some increase in O-input and CO₂-output. The increase of the combustion may be as high as 15 or 20 per cent. (d) The contrast between myxœdema and cachexia strumipriva, and exophthalmic goitre. Increase in the nitrogenous and carbonous metabolism is the striking metabolic symptom of Graves's disease; it is relieved by extirpation of the thyroid. Myxœdema associated with atrophy of the thyroid and cachexia strumipriva due to total extirpation of the thyroid are relieved by thyroid medication. The inference is tempting, nevertheless the facts do not establish a suboxidation. The nitrogenous and not the carbonous metabolism is the prominent feature. It is possible that the influence upon the carbonous combustion may be entirely secondary to the disturbances in the protein metabolism. The fact that on administration of thyroid preparations a certain exaggeration in combustion occurs, is not proof that, with the atrophy of that organ, the combustion would fall below the normal.

The Anæmias.—The essential anæmias were long held to be associated with suboxidation. It seemed natural to question whether an adequate quantity of oxygen could be transported by such small quantities of hæmoglobin. The experimental studies have given the answer in the negative. Under proper conditions of control, subjects with chlorosis exhibit a normal protein and carbonous metabolism, while cases of pernicious anæmia and leukæmia display excesses in the protein metabolism and normal, or supernormal, oxidation. The work of circulation and respiration is notably increased in these subjects.

Cachexia and Marasmus.—One not infrequently meets with instances of these conditions that suggest suboxidation. The patients become emaciated to the last degree, the condition seems to become stationary and, for weeks, the patients remain in a scarcely more than hibernating existence. The body temperature is low, the skin dry, the extremities cold, there is scarcely any digestion, and yet life is prolonged in a most remarkable manner. That their metabolism and combustions are low is not to be doubted, but it is questionable whether they are lower than in simple chronic subnutrition. It is established that individuals subjected to prolonged subnutrition become, in a sense, inured thereto and exhibit a nitrogenous and carbonous metabolism notably lower than in acute starvation. There is nothing to indicate that in the conditions of marasmus and cachexia the relations are different or more extreme than in simple chronic subnutrition, and, although the body under these circumstances operates very economically, we cannot speak of suboxidation.

The hypothesis that diabetes, gout, the so-called lithæmic diathesis, the chronic arthritides, asthma, migraine, eczema and other diseases of un-

known etiology are manifestations of a retardation of metabolism is devoid of foundation.

Superoxidation.—Under this term we understand an increase in combustion in excess of the caloric demands of the body. Since the body habitually burns something more than is needed to supply heat on the minimal physical heat-dissipation, it is apparent that there is a physiological superoxidation that serves as a compensatory arrangement. superoxidation occurs in many diseases. There are oxidations in the protein metabolism, but the chief reaction is hydrolytic cleavage; and oxidation of the products of the hydrolytic cleavage of protein can scarcely be conceived to be susceptible of an exaggeration in the direct sense. Thus, oxidation is a secondary process in the metabolism of protein, and as such is not susceptible of a primary exaggeration, though it might be subject to a primary retardation. Superoxidation affects directly the sugar metabolism. If the carbohydrate input be not sufficient, the fat combustion will become exaggerated so soon as the body glycogen has run low. If the fat ingestion be not sufficient to the oxidation, the body fat will be burned. Since we regard these combustions as of the nature of ferment reactions, the pathological exaggerations are naturally and logically to be ascribed either to an increased concentration of the substrate, or to an excess of the ferments. An important practical concomitant to the superoxidation of sugar and fat is the more or less complete loss of the saving power of sugar and fat for the protein metabolism.

Deficiency of Oxygen.—Asphyxiation is the result of lack of oxygen. Many exogenous intoxications act in part by preventing the utilization of oxygen; such are the nitrites, morphine, arsenious acid, carbon monoxide, cyanides, chloral, paraldehyde, veratrine. A marked degree of deficiency in oxygen cannot be borne for more than a short time. One hears a great deal of the deficiency of oxygen in the production of disease, but when the evidence is analyzed it is seen to be very scanty. In order to establish a lack of oxygen, one ought to possess gas analyses of the respiration or blood. Breathing an atmosphere low in oxygen is accompanied by a high respiratory quotient. In acute pneumothorax and cardiac dilatation, the body suffers from lack of oxygen; the blood content of oxygen and carbon dioxide falls. This situation cannot be long maintained; if compensation be not rapidly established death occurs. In acute and massive hemorrhage a deficiency occurs; this cannot, however, be due to the reduction in the red corpuscles, for it is not possible to bleed an animal over 40 per cent. of its blood even if the fluid be replaced, and there is no deficiency of oxygenation in such a degree of *anæmia per se*.

As a subacute condition, there is evidence that a certain degree of deficiency in oxygen occurs in severe cardiac and pulmonary diseases. In these diseases the efforts at compensation usually are practically successful; what so often kills is the exhaustion produced. In these one may observe an excess of protein catabolism and the appearance of lactic acid in the urine. In some instances of heart disease the blood contains more CO₂ and less O than normal. A favorable tension of O and CO₂ can be shown to exist in the alveoli of the lung, despite which the blood does not seem able to cast out the normal amount of CO₂ or absorb the normal amount of O. Whether the fault lies in an alveolar induration or in a

slowing of the circulation is not known. It does not lie in a deficiency of the respiratory movements.

Just how the partial lack of oxygen affects the organism is not well known. The loss falls first on the protein metabolism, the intermediary products of which appear unoxidized in the urine. The protein catabolism is exaggerated. The body attempts to make up for the deficiency by the utilization of intramolecular oxygen; to what extent this can compensate is not known. In animals under carefully selected conditions of experimentation, an acidosis may be produced. In the anæmias, cachexia, and tuberculosis, in which a deficiency of oxygenation has been popularly supposed to exist, the consumption of oxygen is either normal or excessive. It is possible that exercise would lead to a temporary relative deficiency of oxygen, but under conditions of rest there is no such deficiency.

DISTOXICATION.

Under distoxication are grouped those acts of metabolism by means of which endogenous toxic substances are rendered innocuous. The known reactions of distoxication include conjugation, oxidation, and reduction. In the intestinal putrefaction of the products of protein digestion, a number of aromatic bodies are formed. In the act of absorption they are subjected to alterations that render their slight, though undetermined, toxicity inert. Some of the products of the digestion of protein are quite toxic, yet in the liver this is nullified. If in the dog the portal blood be conducted directly to the vena cava, a severe intoxication is the result. The general application of the theory of distoxication lies in the proposition that the intermediary products of metabolism are more or less toxic and that in the completion of the processes of metabolism to end-products we have what in effect has the value of a distoxication. When also abnormal intermediary products of metabolism appear, they may be distoxicated. Thus cations are withdrawn from the tissues to combine with the anions in experimental acid poisoning, in the acetone acidosis, and in connection with an ash-free diet. When glycuronic acid is derived from glucose it is paired in the body. If leucin and tyrosin are formed by an abnormal intermediary protein metabolism, they will be oxidized to phenyl-oxy-acids; should the amount of the amido-acids be large, a certain rest will be eliminated unchanged. In an analogous sense we may speak of cystinuria and alkaptonuria as abnormalities of distoxication. Pharmacology is filled with references to chemical processes of distoxication. Elimination is obviously an indispensable adjunct to distoxication. Some substances that cannot be chemically distoxicated are harmless if promptly eliminated. The general tendency has been to concede the relative innocuousness of the end-products of metabolism and to refer auto-intoxications rather to deviations in, or the non-completion of, the intermediary processes of metabolism. Under the different headings specific references will, whenever possible, be made to the chemical reactions concerned; we here merely state the point of view.

A hypothesis is now current to some extent, by which distoxication is assumed to be a function of the thyroid, adrenal, and pituitary bodies. This is not assumed to the exclusion of an internal secretion but in

addition thereto. In particular the thyroid body is held to distoxicate the products of renal insufficiency. The hypothesis is not yet upon an exact basis, and, while it may in the future develop into a recognized theory, it does not occupy that plane to-day.

RETENTION INTOXICATIONS.

Under this we understand the retention of the normal end products through insufficient excretion. This leads to accumulation of these substances, and the intoxications are due to their influence upon various tissues and functions. We ought to distinguish the retention of an excess of a normal substance from the accumulation of an abnormal substance. The demonstration of the etiological relations will be obviously much more easy in the second than in the first group.

Jaundice.—It may be accepted that, with the exception of cholesterine, no specific organic constituent of bile is normally present in the tissues. The biliary constituents that may be held responsible for the toxic action of bile are the salts of the glyco- and tauro-cholic acids and the pigments. Glycocoll and taurin are products of protein hydrolysis; the derivation, as well as the chemical nature, of cholic acid is not known. Since the liver is the seat of the final disintegration of hæmoglobin, it has been assumed that the glycocoll and taurin are derived in part from the hydrolysis of the protein moiety in hæmoglobin. The pigments are derived from the hæmoglobin. Following biliary obstruction, the formation of the acids seems to suffer a reduction, but the pigments continue to be formed in the usual quantities.

The toxicity of bile lies largely in the biliary salts, although the pigments possess a certain toxicity, especially evident in the depression of the body temperature. Bile acts as a tissue poison, particularly to the renal, hepatic, and muscle-cells. There is further evidence that it exerts a hæmolytic action. Possibly this may be related to the hemorrhagic tendency so frequently noted in jaundice. The body temperature is reduced, the pulse and respiration retarded,—apparently on account of peripheral influences, since the effects occur following the local application of bile to the surface of the heart after section of the vagus in the curarized frog. There is dilatation of the peripheral capillaries. Large doses cause coma, convulsions, and paralyses. In jaundice we observe clinically, retardation of the pulse, somnolence, albuminuria, sometimes emaciation and cutaneous disturbances, occasionally hemorrhages,—directly corresponding to the experimental findings. In simple instances of jaundice the digestion is little impaired. The temperature of the body may be normal or slightly reduced. Usually there is little disturbance in the nitrogen metabolism, nutrition, or body weight. In prolonged cases the functions of the liver may be greatly impaired, the glycogen of the muscles, as well as of the liver, may be practically absent, and the epithelial cells extensively degenerated. The exceptionally deleterious effects of disturbances of digestion in jaundiced individuals have led several authors to assume a reduction in the activity of the distoxication functions of the liver.

Quite inconclusive is the relationship of hepatic coma to jaundice. Symptomatically the so-called cholæmia resembles experimental biliary

intoxication, but the same symptoms are as frequently seen in hepatic cirrhosis without jaundice. It is difficult to understand how many individuals bear jaundice without marked toxic symptoms. The common explanation that in one case the renal elimination of the bile is sufficient, in another insufficient, is not borne out by urinary observations. In all likelihood the cause of hepatic coma is to be sought less in the toxic effects of the circulating bile than in a disturbance of the metabolic functions of the liver, just as in acute yellow atrophy, phosphorus poisoning, experimental ablation of the liver, and anastomosis of the portal vein and inferior cava. Under this interpretation the prolonged jaundice could lead to grave auto-intoxication through abolition of hepatic function. Auto-intoxications by retention do not remain pure but tend to entrain secondary metabolic auto-intoxication.

Retention of Carbon Dioxide.—Is there an intoxication with metabolic carbon dioxide, connected with disturbances of the circulation and respiration? There is the greatest discrepancy between the apparent simplicity and the actual complexity of the problem. The actual problem must be first defined. (a) The gas-exchange of the body has no necessary relations to dyspnoea. Dyspnoea appears when the gas-exchange is decreased or exaggerated, but often exists independent of any alterations of the gas metabolism. The increased respirations following muscular exertion are not due to the accumulation in the venous system of an excess of carbon dioxide, but to a stimulation of the respiratory centre by substances derived from the muscular metabolism. Not a few chemical substances cause dyspnoea. Many forms of auto-intoxication, in which the gas-exchange is not in the least concerned, give rise to dyspnoea; such are diabetic coma, uræmia, hepatic coma. Lastly, bacterial toxins cause dyspnoea, as seen in pneumonia. (b) Intoxication with carbon dioxide is not necessarily associated with cyanosis, since the fault may lie entirely within the internal respiration. (c) There is no necessary association between the gas-exchange and the carbon-dioxide content of the blood. It is possible for the O₂-input and the CO₂-output, the heat metabolism, to be normal, while the blood is surcharged with carbon dioxide and the cyanosis pronounced. (d) Lastly, deficiency of oxygen must be separated from an excess of carbon dioxide. This is often extremely difficult.

In what diseases and under what circumstances is there an excess of carbon dioxide in the blood and tissues, and what degree of such excess may be properly said to cause auto-intoxication? Oxygen is carried in the blood in chemical combination with hæmoglobin, in small part by physical absorption in the cells and plasma. The arterial plasma is saturated with oxygen. Arterial blood contains about 20 vol. per cent. of oxygen, venous blood some 8 to 10 vol. per cent. In death by suffocation the oxygen is decreased before the death of the animal to less than 1 vol. per cent.

The relations of the carbon dioxide are less certain. It is present in arterial blood to the extent of 30 to 40 vol. per cent., in venous blood about 10 vol. per cent. more. Five-sixths of the gas is in the plasma. In asphyxiated animals the concentration of CO₂ in the venous blood rises but little above the maximum normal of 50 vol. per cent.; this is comprehensible when we realize that most of the oxygen contained in the body is held in the tissues. The mode by which the CO₂ is removed from the tissues and

transported in the blood to the lung is obscure. The most difficult question concerns the nature of the substances with which the CO_2 is held combined in the plasma. Since the stay of the blood in the tissues and lungs is so very brief, association and dissociation must occur with great rapidity. Since the reaction of the blood is neutral, no process can be assumed that is chemically incompatible with this neutrality.¹ The gas has been held to circulate as a bicarbonate, this being formed in the peripheral venous blood, and then during the passage through the lungs reduced to the carbonate, in which form it would circulate to the arterial periphery, there to combine with a fresh quantum of the gas to again form the bicarbonate. This conception cannot be maintained. When a weak solution of sodium bicarbonate, exposed to the atmosphere, attains an equilibrium, it contains about 93 per cent. of the bicarbonate and about 7 per cent. of the carbonate; it requires but slight partial pressure of CO_2 , as low a pressure as 10 mm. of Hg, to check the dissociation entirely. Now the CO_2 in the arterial blood never falls below 25 mm. of Hg and the absorbed gas is equal in the arterial and venous bloods. In addition, a reduction of bicarbonate to carbonate would result in a pronounced alkaline reaction. The inadequacy of the carbonate hypothesis is further illustrated by the fact that, in grave condition of acidosis, the only cation available in the circulation would be ammonia. The role of carrier has also been ascribed to the phosphates. This is impossible, from the fact that the plasma contains but a trace of phosphate. The most recent view allies the CO_2 with alkali-globulin combinations. It is known that the proteins combine with acids or alkalies to form bodies subject to hydrolytic dissociation. The weakest acids and alkalies, however, are able to displace the proteins and CO_2 is able to do so. The conception is that the proteins of the blood plasma are combined with cations and in the venous blood the CO_2 drives out the protein, which then circulates alone until the removal of the CO_2 in the lungs, when it reassociates with the cations. The existence of combinations of protein with hydrogen- and hydroxyl-ions has been experimentally demonstrated. If the so-called alkali-globulin be considered to be an ion-protein, it must be remarked that no one has been able to determine the existence of such combinations in the case of the proteins of blood plasma; and, although considerations in general physiology have made it possible to postulate the existence of such combinations, the present data will not permit us to assume them for the blood plasma. Such a cation-globulin would be subject to a high degree of hydrolytic dissociation, with the production of an alkaline reaction. In short, though the general relations indicate that factors of association and dissociation control the transportation and discharge of the CO_2 , the actual definition of these factors is not now possible.

In asphyxiation the blood-content of CO_2 is increased from one-fourth to one-third, the oxygen-content falls to a trace. Death is due to lack of

¹There is a confusing difference in terminology regarding the reaction of the blood. "Some use the term alkalinity in the sense of titration alkalinity to indicate that the blood will neutralize a certain amount of weak acid. Others employ the term in its strict sense, as developed by modern physical chemistry, to indicate an excess of hydroxyl ions ($\text{OH}-$)," (Howell). The latter view regards the blood as neutral but there seems little doubt that the amount of alkali in the blood as determined by titration is of much importance in regard to the neutralization of acid products.—*Editor*.

oxygen and not to the excess of CO_2 . If an animal be placed in an atmosphere containing 20 per cent. or more of O, 76 per cent. of N, and 4 per cent. of CO_2 (the quantity in expired air), death will occur after a period of narcosis and this represents true CO_2 poisoning. If an animal be placed in an atmosphere too low in oxygen, death will result after a lapse of time and the blood will contain less CO_2 , as well as less O, than normal.

Do disturbances exist in disease which act to reduce the expiration of CO_2 more than the inspiration of O, to the end of CO_2 congestion in the blood? What is the extent of such CO_2 congestion? The conditions are divided into two groups: those in which the respiratory surface is diminished and those in which the action of the heart is disturbed. Recent studies in the physiology of combustion have taught us the extent of the powers of adaptation and compensation residing in the organs of circulation and respiration. In all probability, until these limits are reached, until the unit of blood is not aerated in the unit of time, an auto-intoxication is not to be apprehended.

Of gas analyses, either experimental or clinical, we have few, but it is fairly certain that five conditions may be met with: (a) The O-input and CO_2 -output and the content of the blood in the two gases are normal. This has been found in several cases of emphysema and of heart disease, and indicates a complete sufficiency of the efforts at compensation. (b) The O-input and CO_2 -output are normal, but the CO_2 content of the venous blood is excessive. This has been noted in experimental disturbances of respiration, and indicates that the efforts at compensation were successful only when the level of CO_2 in the venous blood was raised. (c) The O-input is normal, the CO_2 -output reduced, the CO_2 in the venous blood not increased. This has been found in some experimental pneumonias. (d) The O-input and CO_2 -output are reduced. The CO_2 is increased and the O reduced in the blood. This has been found in several cases of heart disease. (e) The O-input is much reduced, the CO_2 -output reduced, the O in the blood much reduced, the CO_2 not increased. This has been found in some instances of experimental pneumothorax. CO_2 intoxication could appear in (b) and (d) alone; intoxication from deficiency in O could occur in (d) and (e). Cyanosis is a sign of lack of O rather than of congestion with CO_2 . Considering the marked powers of adaptation and compensation, what we most need are repeated gas analyses to show what degrees of reduction in O-input and CO_2 -retention in the blood exist, and with what symptoms and signs they are associated.

In the ordinary cases of the types under consideration, the combustions of the body are normal. This does not indicate that there is no CO_2 congestion—the over-flow of a stream will be the same over a high as over a low dam. It does, however, indicate that the input of O is adequate and the total combustion normal; if these subjects are intoxicated it must be from simple CO_2 -retention. In acute experimental dyspnoea the protein metabolism is abnormally increased, the result of deficient oxygenation. The urine contains glucose and lactic acid, the results of lack of oxygen.

In all these there is less to suggest that the subjects are in a direct sense suffering from intoxication with CO_2 than to indicate lack of O. CO_2 -retention is accompanied by an increase in the molecular and ionic concentration of the blood serum—a fact that is not yet understood. It is not

to be denied that there is an intoxication with CO_2 in these diseases, but we should realize how scant is our information of the actual conditions and how indefinitely it points to such an intoxication. The data certainly furnish no warrant for such generalizations as those contained in the statement of von Jaksch, that to CO_2 -retention is to be ascribed the cellular degenerations sometimes seen in this class of cases. That there is a possibility of serious disturbance of metabolism in an organism whose venous blood is overloaded with CO_2 is made obvious by the following consideration. The combustions of the body are acts of fermentation. Accumulation of the reaction products retards the velocity of fermentation. If now the venous blood be so charged with CO_2 as to take up no further gas from the tissues, an excess of the gas would accumulate and exert a retarding influence upon the reactions of combustion. The CO_2 -content of the tissues is known to be much higher than in blood. We do not know that in any circulatory or respiratory diseases the blood-content rises to the height of the tissue-content, or that the latter is increased.

Whether the retention of the products of the respiratory metabolism can be considered toxic apart from the CO_2 is not known. Our present knowledge is negative; other toxic substances have never been demonstrated in expired air.

Retention of Perspiration.—The natural interpretation of the cause of death from extensive superficial injury to the skin, as in burns, rests upon the abolition of the cutaneous function. The chief symptoms are quite like shock. They are not due to the retention of the normal perspiration, as the sweat is almost free of toxic action. There is a widespread notion that toxic volatile substances exist in the perspiration, but this is unsupported by data. The amount of gas-exchange that occurs in the cutaneous functions of higher animals is almost *nil*. The retention of water could not account for the symptoms nor the salts and organic substances known to be eliminated through the skin in the quantities and time concerned. That the simple retention of perspiration cannot be the factor is shown by the experiments in which nearly the entire bodies of men were covered for days with rubber plaster and collodion, without producing any symptoms or signs of illness whatever. That rabbits die after being coated with varnish has been explained as the consequence of the paralysis of the vasomotor system, whereby the heat dissipation is exaggerated beyond the power of compensation.

We are thus driven to the assumption that widespread lesions of the skin cause disturbances in metabolism, which, acting with the disturbances in the vasomotor system, lead to the rapid collapse. We have no idea of the nature of these assumed disturbances in metabolism. That toxic substances are at work is shown by the widespread hæmolyses, the acute degenerations of parenchymatous and muscular cells, and the rapid onset of these lesions and of the clinical symptoms. The hypothesis that the coagulations occurring in different parts of the body are due to an excess of fibrin ferment has not been proved. A burn must have a certain superficial extent in order to be fatal, but this cannot be related to a similar fractional destruction or alteration of erythrocytes. A much more rational explanation would be that the erythrocytes are affected while circulating through the burned areas. Thromboses are prominent in the pulmonary vessels, and these have been held to lead to an acute venous congestion and

arterial anæmia. Acute venous congestion and arterial anæmia due to other causes, however, do not produce the symptom-complex observed in burns.

Retention Intoxication of Intestinal Origin.—Under a strict interpretation of the term, we have no evidence that such a thing as a retention of the intestinal excretions exists. The fæces contain the undigested and unabsorbed residue of the food; the alimentary juices; bacteria and the products of their metabolism; the unabsorbed gases of the atmosphere, mostly nitrogen, and the gases of fermentation and putrefaction; the unabsorbed salts of the diet, and the salts eliminated from the tract and glands; and a small, though undetermined, quantity of metabolic products. The bulk of the fæces is water and bacteria. Of the nitrogen of normal fæces, that of the digestive juices may comprise as much as one-sixth. Now the alimentary tract is, from the metabolic point of view, outside the body. The only true retention intoxication would therefore be such as results from the non-secretion of salt and the juices of the tract and the different glands. Non-secretion of the gastric juice occurs as a nervous abnormality, independent of any lesion; it is not accompanied by signs of auto-intoxication. Of the non-secretion of the succus entericus we know nothing. In all probability, however, it would result simply in starvation. Eliminations of excretions stand obviously upon a totally different footing as regards their relations to auto-intoxications than the eliminations of secretions of physiological function. Abolition of the one results in a damming back; abolition of the other simply in the cessation of the particular function associated with it, though this may entrain a secondary auto-intoxication. The digestive juices in the lower intestines, after their functions are completed, are themselves the prey of putrefactive bacteria, and from this time are apparently to be ranked with the unabsorbed protein. A retention intoxication from non-elimination of salts, particularly of iron and lime, is inconceivable. Of an intoxication resting upon the non-elimination of metabolic products we have no knowledge.

All of the so-called retention intoxications of the alimentary tract are, so far as we have reliable evidence, due to the action of bacteria. Some foods are primarily toxic, others are directly indigestible. These and the bacterial decompositions should not be classed as retention intoxications.

Suppression of Urine.—Under this term we understand the non-secretion of urine. The hypothesis that uræmia is simply a retention intoxication, the result of the non-secretion of the urine, is incompatible with a number of well-determined facts. The anuria of hysteria probably represents a pure non-secretion of urine without notable qualitative changes. There is no reason to believe that the functions of metabolism are repressed or altered; we are simply dealing with a total inactivity of a healthy kidney, an inhibition doubtless of nervous origin. The suppression may be complete; there are many carefully controlled cases in which the anuria persisted for a number of days, in a few cases for over a week. In this type there are no symptoms of intoxication, and when secretion is re-established the urine is normal and the organs exhibit no signs of disease. Attacks of anuria may be of reflex origin; the presence of a calculus in one kidney or ureter may for days inhibit secretion by the other kidney. Here, too, no signs of intoxication are present. Another form of non-secretion without intoxication is seen in acute cardiac dropsy, in which there may

be almost complete suppression of urine. Naturally the kidneys will become diseased from the passive congestion, but for some time they remain practically intact, and the slight amount of urine secreted may present no pathological changes but a trace of albumin and a few casts. This may persist for weeks without any indication of uræmia, and, when later cardiac compensation is reëstablished, the kidneys will often be found practically free of disease. Following the defervescence of fever in the infectious diseases, a marked output of urine often occurs, resulting in the elimination of enormous amounts of organic constituents, whose retention has caused no signs of uræmia. Thus we must concede, that, with healthy kidneys, complete suppression is usually without any signs or symptoms of intoxication.

In renal disease there is no parallelism between uræmia and retention. There are periods of almost complete anuria in subacute nephritis without symptoms of uræmia. Often in subacute nephritis anuria and uræmia go together, but many exceptions occur. A nephritic or cardio-nephritic patient, dropsical to the last degree but free of uræmia, may be freed of his dropsy only to develop uræmia. The hypothesis is advanced that the diuresis, purgation, or diaphoresis, have brought into the circulation the poisons that lay concentrated in the tissues. This explanation will not hold, for unless it be shown that there is some co-efficient of distribution to account for such localization of the urinary constituents, we cannot with our knowledge of the circulation and of the laws of diffusion believe in it. Certainly if that explanation be true, the treatment of the uræmic attack by purging and sweating is dangerous.

One reads a great deal of the retention of particular constituents with elimination of the water. Obviously such a condition could be but transient for the electrolytes, because it would lead soon to a condition of hyperisotonicity that we know to be impossible. The organic constituents could be much longer retained without disturbing the osmotic conditions to a notable degree. But such retention must be analytically demonstrated by investigations under controlled conditions. The present data fail to substantiate the claim.

A general consideration against the theory of simple retention is that it lays upon the kidneys no blame but that of a stoppage of the elimination; it reduces nephritis simply to a plugging of a filtering membrane. Experience with nephritis surely suggests that the disturbances are more than a simple reduction in the power of elimination. Our knowledge of the toxicity of the normal urine does not support the idea that a simple retention would lead to an intoxication. The toxicity of the urine depends upon the fact that the urine is a hyperisotonic solution rich in potassium salts. Even this toxicity will practically disappear if the rate of injection be so slow that the cells have an opportunity to accommodate themselves to the new conditions. As a matter of fact, the whole line of reasoning on the urotoxic co-efficient presupposes a function of distoxication on the part of the kidney,—which is inadmissible in the theory of retention intoxication. It must be insisted that the urotoxic co-efficient of Bouchard, as determined by the intravenous injection of urine into animals, is worthless; not over ten per cent. of the toxicity thus developed is due to the organic constituents; the main toxicity of the urine is that of a hypertonic solution rich in potassium salts.

From the wider theoretical point of view, one can understand how a retention of urine could lead to disturbances in metabolism. If the organic constituents were retained to a greater degree than the water, the result would be to increase the concentration of those substances in the body. Now the processes leading to the formation of these urinary constituents may be assumed to be of the nature of ferment reactions. The obvious result of an increase in the concentration of the products of the reaction would be to retard the reaction, that is, to retard the rapidity of catabolism, and, in addition, to afford opportunities for qualitative variations. This is, of course, a pure speculation, but it is one based upon sound theory.

SALTS. ACIDS, AND ALKALIES.

The proper study of the relations of acids, alkalies, ions, and salts, by physico-chemical methods is quite recent. That they must possess relations of the greatest importance in disease may be confidently assumed. Of direct data almost none are available. Indeed, little of our present knowledge has been derived from studies on higher organisms. In the investigation on the actions of ions and salts on even lower organisms there is much confusion and not a little contradiction. The time has not yet arrived to attempt a discussion of the relations of these factors to disease. At present, our knowledge of the relations of salts, alkalies, and acids in endogenous intoxications is limited to acidosis.

Acidosis.—Under this term we group the disturbances in metabolism that result from the predominance of acids in catabolism. There is in the carnivorous organism always some such predominance, but one easily compensated for. The chief sources of acid are the following: (a) The acids of carbohydrate fermentation in the alimentary tract. (b) The sulphuric and phosphoric acids derived from the catabolism of common protein and nuclein respectively. (c) Lactic acid. (d) The members of the acetone group, diacetic and beta-oxybutyric acids, derived from the fats. (e) Other acids formed in the body—glycuronic, oxalic, uric, aromatic oxy-acids, carbamic acid, and carbon dioxide—are apparently never concerned in the production of an acidosis. For the neutralization of these acids we have the excess of alkali contained in the mixed diet and in drinking-water; when these are insufficient, the fixed cations of the body and the ammonia of the metabolism. Obviously an acidosis may be inaugurated either by a deficiency in alkali or an excess in acids. The result will be the same whether acid be ingested or formed within the body.

Experimentally an acidosis may be produced by the use of an ash- and alkali-free diet. Under these circumstances the sulphuric and phosphoric acids must combine with fixed cations withdrawn from the tissues, and ammonia withdrawn from the urea metabolism. After a certain number of days, no matter how normal the diet in other respects, severe symptoms appear in the peripheral neuro-muscular and central nervous systems, followed by death. In simple starvation the degree of acidosis is not marked, since the protein catabolism is low. Acidosis could occur only very late in a protein-free diet, since here too the protein catabolism is low. The human body cannot maintain the daily catabolism of a hundred

grams of protein in the absence of ingested cations, without the development of an acidosis within a fortnight. In a similar manner, if a mineral acid be administered in quantity equal to that daily formed in the average metabolism, an acid intoxication will develop after a few days.

The acids of carbohydrate fermentation are rarely of pathological importance; they are easily oxidized and are rarely formed in quantities so large as to constitute a menace. There is, however, a possibility that these acids may be responsible for some of the attacks of acidosis seen in childhood. Lactic acid may be derived either from protein or carbohydrate; its constitution is very similar to that of alanine, a derivative of protein hydrolysis. Lactic acid is an intermediary product in the oxidation of glucose. It may theoretically be derived from the oxy-acids of the fatty acid series. In disease, it seems usually to have been derived from protein and sugar. The lactic acid formed within the alimentary tract is, apparently not a cause of acidosis. Most important are the members of the acetone group, which are most often concerned in the production of an acidosis.

The ill effects of acidosis are not clearly understood. There are several chemical possibilities. (a) Acidosis may act simply by virtue of acidity. Difficult as it is to explain how large quantities of acids may be held combined in the blood after a prolonged period of cation withdrawal, the postulated acidity of the blood must be first proven, and this cannot be done by determining that the carbon dioxide is reduced. That the blood may become acid shortly before the death of an animal with sulphuric acid poisoning, has been demonstrated. In any event, an acid reaction of the blood could be only a terminal phenomenon.

(b) Acidosis may act through cation withdrawal. The reserve of cations in the body is limited. It is a postulate of physiology that there are cation-protein complexes in protoplasm. To what extent these might be assumed to be broken up cannot be conjectured. Very soon the supply of fixed cations is greatly reduced or fails, and from thence ammonia alone remains to combine with the acids. Ammonia does from the very beginning combine with a portion of the acid. What we do not understand are the relations of the ammonia to the fixed cations in the neutralization of the anions; no regularity is apparent in the fluctuations clinically observed. How the cation withdrawal results in symptoms is totally obscure. It may be said that the withdrawal of fixed cations leads to protoplasmic disintegrations, to the suspensions of functions, and that the withdrawal of the ammonia from the urea metabolism gives rise to disturbances in the protein catabolism; but from such statements we obtain no exact or definite ideas. If the withdrawal of the cations be the condition underlying the symptoms of intoxication, one does not understand those cases in which the symptoms appear suddenly without having been preceded by a period of cation withdrawal. That the administration of alkalis does not always result in amelioration is no argument for or against this factor.

(c) The acids may possess a toxicity *per se*. A certain toxicity has been made probable for the salts of β -oxybutyric and diacetic acids. Normally the body possesses the power of oxidizing large quantities of these acids. We do not know whether we are dealing with such an overflowing that even the normal powers of oxidation are insufficient, or whether the body

has lost, in part, its power of oxidation; weighty reasons favor the latter.

(*d*) It is theoretically possible that the internal gas-exchange should be disturbed, at least in the severe intoxications; and investigations have shown that under these circumstances the oxidations of the body may fall to less than one-half. Nevertheless, it is doubtful if this be an essential feature of the situation.

CHAPTER XIV.

AUTO-INTOXICATIONS ASSOCIATED WITH PROTEIN, PURIN, CARBOHYDRATE AND FAT METABOLISM.

By ALONZO ENGLEBERT TAYLOR, M. D.

THE digestion of protein is an act of hydrolysis; the end-products are amido-acids. It has been shown that animals may be maintained in nitrogen balance on a diet whose sole nitrogen is present in the form of amido-acids. Under exceptional circumstances, native protein may pass through the intestinal mucosa into the circulations (for example, gelatine, egg albumin, and foreign serum), and be eliminated by the urine. The higher albumoses are absorbable; secondary albuminoses and peptones are readily absorbed. In the dog's stomach ligated at the pylorus, protein will be absorbed without the appearance of more than traces of amido-acids. If such a stomach be deprived of its return-circulation, amido-acids will accumulate in large quantities. From nutrose the human stomach will form amido-acids within two hours.

The processes of protein catabolism may be discussed under the four end-products, urea, ammonia, purin bases, and kreatinin. The purin metabolism is really separate from the common protein metabolism and will be considered by itself.

Urea.—Protein catabolism is chemically very similar to protein digestion; qualitatively we know of few distinctions. In metabolism, as in digestion, the end-products of the hydrolysis are amido-acids, simple and complex. In the aseptic autolysis of organs and in the rapid degenerations of tissue, amido-acids are found in large quantities. It must be further assumed that the dynamic factor is a ferment accelerating a slow hydrolysis that can be demonstrated to occur whenever cells (protein) and water are mixed. The products of protein hydrolysis are subject to a variety of reactions,—disamidation, oxidation, anhydration, and reduction. It is obviously possible that these secondary reactions might be disturbed or insufficient, but our knowledge of these, in so far as they concern the elaboration of the nitrogen, is confined to the steps by which urea is formed from amido-acids.

The liver is the chief seat of urea formation. Perfusion of the liver with the vegetable salts of ammonia, in particular the lactate, carbamate and carbonate, with the monamido-acids that are formed in the hydrolysis of protein, or with the poly-amido-acids like arginine, will result in the formation of urea. Liver pulp is able to convert these several substances into urea. There can be little doubt that these reactions are fermentative, and consist of disamidation and oxidation. In connection with the Eck fistula and extirpations of the liver, the elimination of urea sinks to a trace, while the blood becomes flooded with ammonium salts. We do not know experimentally where the quantities of ammonia (some 12 gm.)

could be secured to furnish the material for the entire urea output; of amido-acid the necessary quantity is easily available. Some ammonia comes to the liver through the portal vein, some is formed in the liver, and a certain amount of amido-substance is withdrawn from the muscles by the venous blood. On purely theoretical grounds it would seem that most of the material should come to the liver from the general system through the arterial blood and that it should come rather in the form of amido-acids than as salts of ammonia.

The liver is not the sole seat of urea formation; the excretion of urea never disappears entirely after the extirpation of the liver or its exclusion from the portal circulation. We have, in the different tissues, hydrolytic and oxidizing ferments, and to a certain extent the reactions probably occur in all tissues. That the kidneys are prominent in the synthesis of urea is not demonstrated.

Ammonia.—The ammonia of the urine was once supposed to bear a reciprocal relation to the urea. According to this idea, if the diet were rich in vegetable salts of the fixed alkalies or in ingested fixed alkali, the urine would contain little or no ammonia; if the diet were poor in fixed alkalies or their vegetable salts, the urine would contain a large amount of ammonia, this being withdrawn from the urea metabolism to combine with the sulphuric and phosphoric acids derived from the oxidation of protein and nuclein, respectively. When herbivora, whose natural urine is very poor in ammonia, are starved, their urine contains notable amounts of ammonia in combination with the sulphuric and phosphoric acids derived from their own flesh. Of the importance of this factor there is no doubt, but it is not even the sole factor. The formation of diacetic and β -oxybutyric acids in the intermediary metabolism is associated with an excess of aminonuria and may, indeed, except in so far as the acids are reduced to acetone, be measured by it. Normal urine contains a trace of acetone but neither of the acids. The absorption from the alimentary tract of the acid products of fermentation is accompanied by the binding of ammonia, of small moment normally. It is furthermore certain that if the formation of urea is to be regarded as the conversion of ammonium salts into urea under the influence of enzymic acceleration, a certain amount of ammonia must remain in the circulation for the simple reason that the reaction is an incomplete and reversible one. This ammonia circulating in the blood-plasma would naturally be eliminated by the kidneys. The elimination of ammonia is subject to rather marked fluctuations, even when the subjects are upon a constant diet. Masked pathological augmentations are in all probability connected always with acetone acidosis.

Kreatinin.—Blood and muscles contain small quantities of kreatinin and larger quantities of the parent substance, kreatin; the urine contains kreatinin alone; kreatinin of urine is identical with that of muscle. Kreatin on administration is eliminated in part unchanged, in part as kreatinin; a fraction however is lost in the metabolism. It is possible that it has been converted either into purin or into urea. The natural interpretation of these relations would be that kreatin is formed from some protein of muscle and then elsewhere converted into kreatinin. The amount of kreatin and kreatinin is greater in the exhausted than in the resting muscle, but this does not appear to show itself in the total nitrogen or kreatinin output. Kreatinin, on hydrolysis in an alkaline reaction, is

split into urea and methyl-glycocol, and this has been regarded as one of the possible sources of urea. Possibly the amounts concerned are too small to be noted under the conditions of the experiments.

Disturbances in the Protein Metabolism Dependent on the Input.—A diet devoid of protein means nitrogen starvation. If carbohydrate and fat be present in excess of the quota required for the maintenance of the body heat, the nitrogen output (urea) will sink far below the output in starvation. Insufficiency of protein is unfortunately of frequent occurrence. Whether any people live for any length of time upon a ration containing less than 1 oz. (30 gm.) for a body weight of 150 lbs. (65 kilos)—the lowest known experimental figures—is not known. The results lead, so far as we know, to no auto-intoxication. Subnutrition is of grave consequences to children, less harmful to the aged. The most prominent result is the lowering of the resistance, particularly to the infections (starvation may be shown in animals to be accompanied by a reduction in the antibacterial properties of the blood); *i. e.*, the full employment of the powers of compensation with respect to the diet diminishes the further available powers of compensation. Pronounced weakness attends such a diet, but prompt recovery follows on return to a normal diet. Important is one metabolic sign which those underfed in protein share with the convalescent,—the retention of nitrogen on a ration that would not be sufficient to maintain a balance in the same individual in health and good nutrition.

The results of an excess of protein have not been fully investigated. A man of 160 lbs. (70 kilos) can digest probably not over 2.2 lbs. (1 kilo) of protein per day. When an individual in good nutrition is placed upon a heavy protein diet, the usual result is that catabolism is exaggerated, so that the output equals the input and the body is upon a nitrogen balance. In an individual of superior powers of digestion, under forced feeding with carbonous as well as nitrogenous food, an appreciable retention of nitrogen may occur. This is not permanent for the healthy adult; it disappears after the forced feeding is suspended, the products being eliminated by the urine. Such a retention of nitrogen is very easy to attain in children, but here it is largely permanent, represents a true flesh-mast, and is proportional to the growth and not to the input. The same thing is true to some extent of convalescents; until they have regained their normal musculature and body weight, the retention is likely to be permanent. In the aged such a retention is scarcely attainable.

This retention is in the form of protein. It is in part carried in the blood plasma, the protein content being increased over the normal. (No increase in plasma protein leads to albuminuria.) The protein of the blood plasma is not a constant but a fluctuating quantity, being lowered in sickness and subnutrition and raised in supernutrition. In part, however, the excess of protein is carried in the tissues, especially in the muscles, which seem to possess powers of compensation. The muscle cells shrink in sickness, as has been shown by measurements; and chemical analyses have shown, under these circumstances, a reduction in the nitrogen and an increase in the water. Supernutrition will result in an increase in the size of the muscle fiber, and an increase in the nitrogen and a reduction in the water. We have no knowledge that the retained nitrogen is carried in any other form than as protein. This retention simply indicates an excess in

the individual's powers of digestion and absorption over the power of disassimilation; when the input falls below the level of catabolism, the excess will be gradually removed until the individual is restored to the natural balance.

Does the excessive ingestion of protein lead to abnormalities in the metabolism, to auto-intoxication? There is now current in the laity, and also among many physicians, the idea that the heavy consumption of protein is harmful, indeed the cause of widespread disease. It is supposed to be responsible for gout, innumerable ill-defined diatheses, arteriosclerosis, nephritis, a large number of skin diseases, and, by extreme vegetarians, for an intoxication *sui generis*. For all these claims there is no adequate basis. The excess of protein is hydrolyzed, the body displays the greatest vigilance in keeping the system in a nitrogen balance; to accomplish this means an expenditure of energy, which might be conceived to lead to some disturbance of function. With an increased protein ration the protein residue in the intestine is increased, affording a greater substratum for putrefactive processes. The products of the excessive protein metabolism have all to be eliminated, and this imposes an increased task upon the kidneys. If the products of protein metabolism be toxic, this toxicity must be exaggerated under an excessive protein diet. These considerations make it apparent that the excessive ingestion of protein might tend to alterations in metabolism and elimination that would constitute auto-intoxication. The question is again one of fact. Large classes have, since time immemorial, been accustomed to an excess of protein food. We have little exact information that this has produced disease. We have no exact evidence that a moderate excess of protein is the sole and direct cause of any known disease. There are, however, individuals who under such conditions are not well, suffer from headache and insomnia, have little spontaneity and initiative, are sluggish and uncomfortable, possibly morose, and who are relieved by reduction in the protein of the diet. There is, apparently, for each person a certain excess of protein that cannot be tolerated without disturbances in the sensations of health. Excesses of protein are borne badly by infants. What is commonly regarded as auto-intoxication following the excessive use of meat is usually indigestion and not a disturbed metabolism. The limits of digestion of protein are often more narrow than those for starch or fats.

Disturbances of Protein Metabolism Independent of the Input.

—The retention of protein is seen only under few conditions. In youth this is of obvious purpose and is proportional to the growth. Following illness, subnutrition, and starvation, the body retains protein until it has returned to the normal. Under forced feeding, the body retains protein so long as the forced feeding is maintained. There is a current idea that the metabolism of the protein is often incomplete. Following the cessation of fever in the infectious diseases, an increased elimination of urea may be observed. It is believed that during the fever the catabolic processes were incomplete and that following the defervescence they are completed and the excess of urea eliminated. This explanation, like the one defining the condition as simply a retention due to renal insufficiency, is not supported by experimental work. The phenomenon is probably to be explained by the breaking down of the excessive number of leukocytes and other cells,

thus corresponding to the observed increased output of purin bodies and phosphoric acid.

Excess of Protein Metabolism.—This is seen particularly in six groups of sickness: fevers, infections, neoplasms, the essential anæmias, exophthalmic goitre, and intoxications. As a rule in exaggerated protein catabolism, the secondary reactions are sufficient, and the nitrogen appears the form of the normal end-products. Sometimes, however, the intermediary products, amido-acids, appear in the urine. In some cases of acute atrophy of the liver, the nitrogen output in the urine will be very low at a time when the circulation is flooded with amido-acids; under these circumstances, these, as well as the end-products, fail of elimination.

Fever, per se, increases the disintegration of protein. The high temperature increases the cellular disintegration and causes some cellular degeneration, the products of which are thrown into the circulation and there act to produce an increase in the nitrogen output. All fermentative reactions are accelerated by increase of temperature within certain limits, and it is theoretically possible that the increased combustions in simple fever are the direct result of this. To the possible objection that an increase in the temperature over the normal could not be supposed to accelerate a physiological function, it must be replied that for every ferment in the human body the optimum temperature is a number of degrees higher than that of the body.

The febrile *infectious diseases*, especially of acute type, are accompanied by very marked increases in the protein catabolism. The relations vary for different days and periods; but if the input and output for the entire course of the disease be obtained, the fact in most instances is striking. Individuals of lean constitution are affected less than large, well-nourished subjects. The loss is greatest during the earlier stages of the disease. Rarely there is no nitrogen deficit. As a rule, the exaggeration of the protein catabolism is more marked in the fevers than is the increase in the combustion of sugar and fat; in moderate fever the combustion of fat and sugar is often normal. The deficit may mean a loss of protein to the body, but by increasing the diet the deficit may be abolished (even in the child), though it is usually possible only to minimize the loss. To accomplish this, much greater quantities of sugar and fat are necessary than would be needed in the normal subject. In other words, the protein-saving power of sugar and fat is reduced. An increase of the ingested protein in the febrile subject is not followed by an increase in the nitrogen output, at least not to the same extent. Thus, while sugar has lost a part of its power of saving protein, protein in the diet has acquired a power of sparing protein in the metabolism,—which is best explained by the assumption that there is, as in subnutrition, a protein-deficit in the circulation which the excess of ingested protein simply makes good. Subjects with moderately severe infections of acute course will commonly lose from 5 to 8 gm. of nitrogen daily; severe cases from 10 to 15 gm.; in extreme cases the loss may be as high as 20 gm.

The afbrile infections have not been well studied. In chronic cases of tuberculosis, malaria, and syphilis, without any measurable fever and despite good feeding, we often see rapid and extensive emaciation of the muscular system, which must be accompanied by a nitrogen deficit. In lesions of the nervous system, as transverse myelitis, we often observe a

rapid and extensive muscular wasting; the muscle cells degenerate under the absence of the normal trophic influences, and the protein derived from their protoplasm would be disintegrated just as though it were an excess protein ingested.

In *exophthalmic goitre* we have a striking illustration of metabolic exaggeration. Associated with an excessive or perverted functioning of the thyroid body, the protein catabolism is exaggerated. There is a deficit of nitrogen, and strenuous forced feeding (up to 60 cal. per kilo per day) may not maintain the body weight. Despite increased heat dissipation, the body temperature is normal or even increased. The exaggeration of the protein catabolism, while marked, is less extreme than the increased combustion of the carbohydrates and fats. The exaggeration of protein catabolism may represent simply an attempt at a compensation for the exaggerated carbonous metabolism, an aid in the heat production. Possibly the condition may resemble starvation; since the sugar and fats are so abnormally burned, their sparing power on the protein metabolism would be wanting, just as in subnutrition with a low carbohydrate ration. It may be possible that the exaggeration of the protein and the greater exaggeration of the carbonous metabolism are the common results of one cause. The thyroid body is now believed to possess an internal secretion that acts as an accelerator of protoplasmic combustions, the administration of thyroid preparations and an excessive activity of the thyroid body lead to further exaggerations in the combustions. In other words, the thyroid body is conceived to supply a substance that acts as a zymo-excitor to the fermentative reactions comprised in the protein and carbonous metabolisms.

The exaggerations that are observed in association with the essential *anæmias* are not dependent upon the *anæmias per se*, but upon the conditions underlying them. Simply *anæmia* and *chlorosis* present a normal metabolism. In *pernicious anæmia* and in *leukæmia*, the protein metabolism may be for long periods notably exaggerated and accompanied by a loss of body protein. All cases do not exhibit it at all times; one may obtain normal values, or indeed a nitrogen retention and the accumulation of flesh, during some periods of the disease. In the *anæmias* the exaggeration of the protein metabolism is not accompanied by a notable increase in the combustion of sugar and fat. A study of these diseases has led to the assumption that they are of toxic origin, and with this the exaggeration of the protein disassimilation is in good accord.

In the *cachexia of malignant diseases* there is a notable exaggeration of the protein catabolism. It may be absent during periods of very chronic progress, but during active growth a nitrogen deficit is present, and this does not seem to be easily controlled by the ingestion of a luxurious carbon ration. These cases incline also to an excessive combustion, and may indeed, exhibit marked superoxidation. The relations of the tumor mass might be of influence. The reproduction of neoplastic cells requires protein and this, if extensive, might be expected to tend to a nitrogen retention. The neoplastic cells, however, are short lived and frequently degenerate *en bloc*, and this would lead to a nitrogen deficit.

Intoxications.—Poisoning with exogenous substances (phosphorus, arsenic, chloroform and others) is accompanied by an exaggeration of the protein catabolism. As a rule the secondary oxidations are sufficient to

convert the amido-acids into the normal end-products, but in many cases these are to be found in the urine, while in the liver and blood amido-acids may be found in quantities. The urine contains large amounts of ammonia combined, not with acids of the acetone group, but rather with lactic acid and mineral acids derived from the disintegrated protein. The combustion of sugar may be reduced during the last periods of the intoxication. The respiratory exchange has been determined to be normal. Glycogen disappears from the liver and to a large extent from the muscles. The limit of assimilation for sugars is reduced, but the injection of phloridzin will not provoke glycosuria. The liver retains the power to conjugate aromatic bodies, but has lost the power of oxidizing benzol. The kidney loses the power of forming hippuric acid from benzoic acid and glycocoll.

The brunt of the intoxication falls upon the protein metabolism. The excessive hydrolysis of protein is associated with exaggerated autolysis of the cells, particularly of the liver. That this postulated exaggeration of the autolysis of the liver occurs, is shown by the experimental fact that the aseptic postmortem autolysis of the liver is much more rapid in the case of phosphorus poisoning than in the normal liver. In a word, phosphorus poisoning acts like a fermentation. Acute yellow atrophy of the liver and acute pancreatitis resemble, in their chemical details, phosphorus poisoning, and we are justified in the assumption that the acts of intoxication are similar. Whether these be due to bacterial or endogenous ferments cannot be stated.

The mechanisms by which these exaggerations of the protein metabolisms are carried out have not been investigated for the various conditions. The following considerations deserve mention:

The Fever, Per Se.—This is able to exaggerate to some degree the catabolism of protein.

The Leukocytosis.—Associated with this is an excessive cytolysis, the products of which would enter the circulating plasma and be there subject to the same hydrolysis as protein from the diet. How extensive this may be we do not know, but in certain diseases it should not be a negligible quantity.

The Cellular Exudates.—These, in pneumonia and septic collections, are unquestionably of great importance. During the period of resorption, the subject of a croupous pneumonia may resolve and disintegrate a kilo or more of cellular material, and in such cases the highest figures are obtained. The disintegration of such exudative collections could account for the protein deficit only during the stage of resolution, not during the stage of formation. Now since the phenomenon is present during the stage of formation, when a nitrogen retention might have been expected, it is obvious that during that period some other active agent was in operation. The mechanism of the exaggeration of protein catabolism is here also simply that of flooding the circulation with the protoplasmic protein, which is then hydrolyzed like any excess however derived. Closely allied is the absorption of *transudates*, whose protein is thus added to the circulation. These fluids also contain urea, so the figures seem more striking than they really are, because this urea only balances a previous retention.

An important factor is the *toxic cellular degenerations*, the exaggeration of the normal autolysis. In poisoning by phloridzin, toluylene-diamine,

nitro-benzol, and potassium chlorate, in addition to those previously mentioned, we find extensive and very rapid cellular degenerations. The writer has recently seen cases of extreme degeneration of the liver occurring within three days of a chloroform narcosis. Similar conditions are found in acute yellow atrophy of the liver and in acute pancreatitis. These degenerated cells become an excess in the circulation and are then hydrolyzed and burned like any other excess of protein. Furthermore, there exists, particularly in the muscles, an emaciation of the cells without degeneration. That these cellular emaciations and degenerations exaggerate the protein metabolism by casting into the circulation an excess of protein is shown by the fact that it is not possible by the administration of any amount of carbohydrate to spare the nitrogenous output as much as in health.

Lastly, it is possible that there may be some direct influence on the reactions of the hydrolysis of protein, some accelerating influence of the nature of a zymo-excitor. The hypothetical substance could be derived from the metabolism of the bacteria, or less probably from the necrobiotic cells. It is conceded that this is a pure hypothesis, but it is high time that hypotheses derived from general chemistry and physics should receive some attention in these matters and not be entirely excluded by mechanical or vitalistic speculations.

It is clear that an exaggeration of the protein catabolism bears no constant relation to any abnormality in the processes of carbonous combustion, and in particular one may not infer from the existence of such an exaggeration that a suboxidation is present. The failure to understand this has been responsible for much confusion.

Cystinuria.—Cystinuria is a hereditary abnormality of the protein metabolism. Cystin is derived from protein; it has been recovered following the acid hydrolysis of kreatin, hair, serum albumin, and edestin; it has been found in the liver and kidney and among the products of the digestion of fibrin with pancreatin. The most obvious chemical mechanism for the formation of cystin in the body would be to assume that cystein is a normal product of protein disintegration, that it is oxidized to cysteinic acid, and this then converted into taurin by the splitting off of carbon dioxide, probably as a fermentative reaction. Under the pathological conditions in cystinuria, the cystein instead of being converted into taurin is converted into cystin by the union of two molecules, a sort of condensation. The administration of cholic acid to the cystinuric produces no increase in the cystinuria.

Cystinuria is usually accompanied by the excretion of pentamethylenediamine and tetramethylenediamine. Since these ptomaines are usually found as the results of putrefaction, the first inference was that the cystinuria was of intestinal origin. Cystinuria has been observed unaccompanied by ptomainuria; the ptomainuria occurs in cholera and other conditions independent of cystinuria. These diamines may be recovered from the products of the tryptic or peptic digestion of protein (due to the fermentation of lysin and ornithin) and there is no reason why they may not be of metabolic derivation. Instead of terming cystinuria a condition of intestinal origin, it were better in these cases to locate the origin of the diamines in the tissues. Cystinurics are deficient in the faculty of oxidizing amido-acids.

In proportion to the quantity of the cystin, the neutral sulphur is increased at the expense of the sulphuric acid. The amounts that may be eliminated are sometimes quite large, more than a gram per day. A synthetic cystin-uramino acid is known, that is possibly contained in the normal urine. Occasionally calculi form in the kidneys or bladder. There are no symptoms of auto-intoxication and no known sequelæ except calculi. The condition is not affected by any constituents in the diet; in particular, meat does not seem to cause any noteworthy increase.

Alkaptonuria.—Idiopathic alkaptonuria is a family disease, consisting in the elimination in the urine of two aromatic derivatives, trioxypheylpropionic and dioxypheylacetic acids. It was first thought that these were formed from tyrosin in the alimentary tract and then absorbed; experimental studies are opposed to this, as is also the occurrence of the condition in the new-born infant in an alkaptonuric family. Tyrosin is formed in the intestine as an end-product of tryptic digestion. From it phenol and cresol are derived by bacterial action through a reaction of disamidation. Tyrosin is formed in the body as an intermediary product of protein metabolism. If the amount be excessive, as in extensive tissue autolyses, tyrosin appears in the urine; otherwise it is oxidized. A normal individual is able to oxidize notable amounts of ingested tyrosin, and the abnormality in alkaptonuria consists, then, in the inability of the body to oxidize the tyrosin derivatives beyond the stage of dioxypheylacetic acid, which is eliminated unchanged. The reaction is one of fermentative order; a ferment is known in plants that converts tyrosin into dioxypheylacetic acid. The inability to further oxidize dioxypheylacetic acid is seen in occasional cases of hepatic cirrhosis, tuberculous peritonitis, and diabetes. The abnormality is unquestionably situated in the intermediary protein metabolism. This anomaly is usually the only metabolic abnormality present and the subjects are entirely well.

Uræmia.—Uræmia is here classed, without adequate experimental or chemical evidence, as an auto-intoxication of the protein metabolism, simply because this is the direction of least resistance. The carbonous metabolism is known to be normal. That the condition is an auto-intoxication is provisionally proven by the resemblances of the symptoms to well-known exogenous intoxications. As stated, uræmia cannot be regarded as a simple retention intoxication; it is likewise not possible to incriminate any known normal constituent of the urine.

Urea.—That urea cannot be the cause of uræmia is shown by its comparative innocuousness. A toxic action is obtained only by the injection of large quantities, and the withdrawal of water. The injection of urea is followed by a vasomotor dilatation of the vessels of the kidney, but this has no bearing on the conception of uræmia. Animals bear such treatment without the slightest apparent result. A case has been reported in which, on the day following an eight-day anuria, nearly 150 grams of urea were eliminated. There is no parallelism between the occurrence of uræmia and the urea content of the blood. There may be retention without uræmia, uræmia may set in without retention. There is no relation between uræmia and drowsy. In subacute nephritis there is usually some retention during periods of uræmic intoxication, but this is coincident.

Ammonia.—The theory that ammonium salts are the cause of uræmia is disproved by the simple fact that no such amounts of ammonia are to be

found in the blood or urine. If it were true, then in acetone-acidosis we would have uræmia, since here we have the largest quantities of ammonia in the blood and urine, and it would be immaterial for the causation of an intoxication whether the ammonia were withdrawn from the urea metabolism to be combined with the fatty acids, or originated in a fermentative decomposition of urea or in its non-formation. That the ammonia might be supposed to circulate as the hydroxide is out of the question. Uræmia cannot be produced by the injection of salts of ammonia.

Kreatinin and Kreatin.—The extractives are not responsible for uræmia. They are not retained prior to the attack. In animals under ether anæsthesia, the application of kreatinin to the exposed cortex causes spasms and convulsions, but since these may be provoked by innumerable substances, the conclusion that kreatinin is the poison in uræmia is unwarranted. The idea that the extractives bring about a condition of eclamptic irritability is not in harmony with the fact that the electrical irritability of the cortex is not increased after ligation of the ureters. Kreatinin and kreatin are not increased in the urine or blood during uræmia.

The Salts.—Equally unsatisfactory is the theory that the toxic agents lie in the salts, particularly of potassium. If the salts be injected slowly and not in hypertonic solution, the tissues will accommodate themselves to very large quantities. Now in nephritis the accumulation is slow and hypertonicity is never produced, water is always retained in proportion. The more recent studies of the actions of salts have given no support to the saline theory of uræmia. There is no constant retention of salts in uræmia, no constant or notable hypertonicity of the blood, and the injections of hypertonic solutions will not provoke uræmia in nephrectomized animals.

In acute and subacute nephritis the occurrence of uræmia seems to run parallel to the impermeability of the kidneys; in chronic interstitial nephritis no such relation is observed. We are entirely ignorant of the nature of this diminution of secretory power. There is no constant relationship between uræmia and the histological lesions in the kidneys.

We are thus led to the conclusion that the causation of uræmia is to be sought neither in the retention of the total urinary secretion nor in the retention and toxic action of any known constituent. Consequently, since the end-products of protein metabolism cannot be held responsible, we must look for the agent in the intermediary metabolism. Three possibilities suggest themselves:

(a) The functions of the kidney include an act of catabolism in which some intermediary product is converted into an end-product; in nephritis this function would be to a certain extent non-operative and an intoxication would result. This avoids entirely the difficulty of explaining why no intoxication is produced in the functional anuria. The studies on the total protein metabolism in nephritis have given very irregular results, and it is possible that an intoxication from some intermediary product could occur without leading to a marked nitrogen retention.

(b) A metabolic anomaly lies behind the kidney, associated with the renal lesions as cause, effect, or correlation. This is a hypothetical proposition; we possess, however, a suggestive analogy. The intoxication that follows the switching of the liver out of the circulation is in many respects

like uræmia. An intoxication may be due to the ammonium carbamate and other ammonium salts, but the injection of these salts will not yield the full symptom-complex. The Eck fistula is well borne if the animal be given a little protein; coma and death occur early if much protein be administered; behind the known alterations is some abnormality in the intermediary metabolism (not a simple acidosis), and therein lies the unknown toxic agent. If now the hepatic artery be ligated, death occurs within a few hours under most excessive acidosis (not the acetone group), for which the available ammonia is insufficient. The loss of the hepatic circulation entrains greater disturbance of metabolism and intoxication than does the loss of the portal circulation, with its concomitant approximate abolition of the formation of urea.

(c) The kidneys possess an internal secretion necessary for the intermediary protein metabolism, the absence of which is followed by metabolic disturbances ending in intoxication. This theory avoids the difficulty of explaining the non-occurrence of uræmia following prolonged total retention; it is not irreconcilable with the observations that in some diseases, like pernicious anæmia, no uræmic symptoms appear, although the kidneys present extensive degenerations, while on the other hand uræmia may appear in some renal intoxications, as in cantharides poisoning, that are accompanied with trifling lesions. The experimental findings have, in general, tended to speak in favor of this hypothesis; after nephrotomy, life is prolonged and central symptoms ameliorated by the injection of renal extracts.

Pertinent in this connection is the question of specific nephrotoxication, and the facts may be stated thus: it is not possible in animals to produce autonephrotoxins or isonephrotoxins; the injection of the blood serum of an animal with nephritis (spontaneous, or due to the injection of heteronephrotoxic serum or of chromium) into another animal is followed by signs of transient nephritis; chronic nephritis or uræmia is not established. It is apparent that nothing has been learned as yet that could be applied to the problem of uræmic intoxication. But the toxicity of the serum of animals with renal lesions for the kidneys of healthy animals, warns us that the relation of the kidney to the circulating blood is to be considered no more closely than the relation of the blood to the kidney.

Conceding that we possess as yet no qualitative demonstration of the theory that the cause of uræmia lies in the intermediary protein metabolism, are there quantitative variations? It is known that peculiar fluctuations in the nitrogen occur in nephritis; periods of retention are followed by periods of deficit, and these without any regular relation to the dropsy or to the symptoms of uræmia. No one can work with the nitrogen metabolism of nephritis without being convinced that there is something wrong which is not expressed in the end results except in an incidental manner. The influence of various diets on the metabolism of nephritis is not known; we have only superficial studies on the relations of different diets to albuminuria. The albuminuria is of no metabolic consequence to a nephritic who has moderate powers of digestion. An excess of uric acid is often found in the blood in nephritis, but normal values are obtained in the urine. There is no evidence for the theory that nephritis is accompanied by a retention of purin base. Acidosis is not present in uræmia, nor is the urinary elimination of ammonia particularly high.

Overexertion.—Within recent years we have learned of the existence in human beings of a condition termed autotypyphization, apparently of autotoxic origin, resembling the *surmenage* of animals. It is seen following prolonged and abnormally heavy exertion. Unlike the *surmenage* of animals, it seems to have no relations to the diet. The symptoms are fever of irregular type, headache, muscular prostration, albuminuria, sometimes an elimination of lactic acid, probably a slight excess in the nitrogen elimination, and often cardiac dilatation. Possibly the conditions that have been described in foot-ball players following severe games are related to *surmenage*. The theory that the condition is due to an excess or abnormality in the kreatinin metabolism has failed of confirmation by urinary analysis. The symptoms and attendant circumstances suggest an auto-intoxication but we have no exact knowledge of it. The acid intoxication that occurs in herbivora, following excessive exercise, is a different complex.

AUTO-INTOXICATION ASSOCIATED WITH THE PURIN METABOLISM.

Concerned in this metabolism are the substances derived from the purin nucleus; uric acid; and several bases, xanthin, hypoxanthin, adenine, guanin, and three vegetable bases, caffeine, theobromine, and theophyllin, all methyl xanthins. The purin input consists of the nucleins and the preformed purin bodies contained in the diet, and the bases contained in tea, coffee, and cocoa. The purin input may vary with the diet, from nothing to 15 grains (1 gm.) per day. The nuclein is hydrolysed in the alimentary tract and split into purin bases, a pyrimidin complex, a pentose and phosphoric acid; the purins thus derived join, in their absorption, the preformed purin of the diet. Whether any purins are oxidized or destroyed in the intestinal tract is not known. After absorption the purin may be used in the synthesis of nuclein, oxidized or eliminated unchanged. Ingested uric acid is eliminated in part unchanged, in part as urea; xanthin, hypoxanthin, and adenine are eliminated in part unchanged, in part as uric acid; the methyl-purins (caffeine, theobromine and theophyllin) are eliminated as methyl-xanthin and are not oxidized to uric acid. In a certain sense, therefore, all these bodies may be termed intermediary products; to what extent conversions occur we do not know. Obviously therefore the purin output on an ordinary diet comprises an exogenous and an endogenous fraction. For the purposes of clinical experimentation the exogenous purin may be excluded by the employment of a milk diet.

Is the purin output derived solely from the input and nuclein catabolism or is uric acid formed by synthesis? In other words, does the endogenous purin proceed entirely from the nucleinic metabolism, or is purin otherwise formed? The hypothesis that uric acid may be formed by oxidation without the nucleinic metabolism is old, but has never been confirmed in an exact manner. Recent investigations however have shown that hypoxanthin is formed during the period of exercise of muscle, an important observation whose bearing on the practical problems is not yet definable. Purin may be derived from purin and nuclein in the diet, from urea and lactic acid, and from the catabolism of nuclein; purin

bases may be eliminated as derived from each of these three sources; they may also be converted into uric acid. Uric acid may be derived from the purin and nuclein input, from the nuclein catabolism, and by synthesis; uric acid may be eliminated as derived from these sources and may also be converted into urea.

There is no parallelism between leukocytosis and uric-acid output. The circulating leukocytes are but a fraction of the total leukocytes, and the assumption of a regular cytolysis proportional to the total increase is unfounded. In pneumonia the uric-acid output is parallel with the resorption of the exudate, not with the circulating leukocytes. The excess of uric acid to be seen in some cases of nephritis cannot be explained on any theory of leukocytosis or lymphatic activity. The excess of uric acid in dogs with an Eck fistula, following cauterization of the liver, and in acute yellow atrophy of the liver and phosphorus poisoning, cannot be reduced to the lymphatic system. Leukocytosis and an increased output of uric acid are correlated results of a common cause, but the latter can occur without the former. Our knowledge of the nuclein content of different tissues alone renders very improbable any theory that rests the production of uric acid upon the cytolysis of circulating lymphatic cells alone or even on the cytolysis of the whole lymphatic system. The purin metabolism is concerned with the nuclein of the entire body and not specifically with that of the lymphatic system.

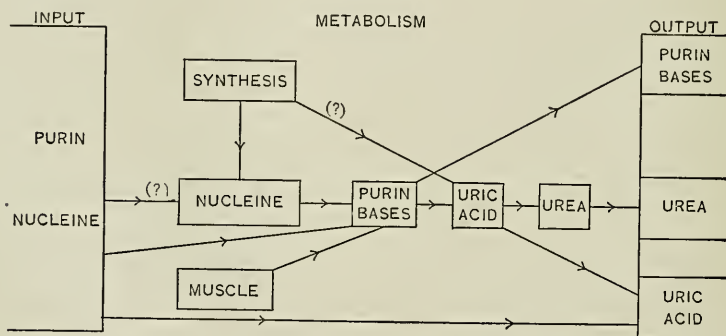
Is the purin absorbed from the alimentary tract utilized for the synthesis of nuclein; is it combined with the pyrimidin derivative, pentose, and phosphoric acid, to form nucleinic acid? This is a crucial question. In health the intensity of the purin metabolism is quite constant. If the ingested purin be utilized in the synthesis of nucleinic acid, less would be required from other sources. That the body can easily synthesize purin directly is shown by the formation of nucleinic acid in the hatching chick, by the regular functioning of the purin output on a milk diet, and by direct prolonged experiments on growing animals. If now exogenous purin be utilized in the synthesis of nuclein, the exogenous purin of a particular diet cannot be subtracted from the total purin output in order to arrive at a figure for the purin output of endogenous origin. Since the increase of a purin input is followed by an increase in the output, it follows either that the purin metabolism behaves like the common protein metabolism—an excess of the substrate results in an acceleration of the catabolism—or else the absorbed excess is simply eliminated directly. This question of the utilization of ingested purin has not been definitely decided. In the writer's opinion the present evidence indicates that exogenous purin is not utilized in the synthesis of nuclein; the purin and pyrimidin rings are synthesized *de novo* from protein, the pentose from hexose, and these then combined with phosphoric acid to form the nucleinic acid. In all probability the purin metabolism, though it concerns a group of structures, is subject to exaggerations whenever abnormal excesses of cytolysis occur.

The seat of the oxidation of purin bases to uric acid is not single, although the liver is particularly active in this function. Birds and dogs when deprived of liver are still able to secrete uric acid. That the lymphatic structures have the power of effecting this oxidation has been experimentally shown. The older theory that the kidneys were the chief

seat of this oxidation is now entirely discredited. Of the relative preponderance of the liver and lymphatic system in this function we know nothing. This reaction is to be regarded as a fermentative oxidation, and we are not surprised that it should not be localized in one organ. The synthesis of uric acid occurs in birds only in the liver, and the same has been made very probable for the mammalian organism. The oxidation of uric acid to urea has not been brought into definite connection with any organ. The liver, kidney, and muscle of the dog and pig have the power of thus oxidizing uric acid. The oxidation of uric acid to urea is probably not a pronounced phenomenon. When a large single dose of uric acid is ingested it is converted in part into urea, but it is not known to what extent such conversions occur in the course of metabolism. It is certain that the purin output represents the larger part of the purin metabolism, *i. e.*, an end rather than an intermediary product.

Now these facts, apart from the light they may throw upon this complex problem, demonstrate one point of practical importance in the interpretation of urinary analysis. Without the purin input being known the estimation of the uric-acid excretion is worth nothing as evidence of the state of the purin metabolism. But with the purin input known (or excluded), the estimation of the uric acid alone, or of the total purin, cannot be used to determine whether the purin output be normal, increased, or decreased, the purin metabolism normal or abnormal. The following diagram illustrates the facts of the purin input, metabolism, and output:

FIG. 4.



When one realizes that the output of uric acid and nuclein is related to respectively three and four variables, it is apparent that by no simple estimation of the output of uric acid or the total purin can a conclusion be drawn of the magnitude of nuclein metabolism, unless we control the other variables, which we are not able to do. We possess to-day no analytical, or, for human organisms, experimental method of determining the magnitude of the purin metabolism or the relations of output to metabolism.

There is no constant relation between the purin and protein metabolisms or between the purin output and the urea or nitrogen output. It is possible by an arbitrary modification of the diet with respect to the ingestion of common protein and nucleinic tissue to vary the ratio within very wide limits; the urea uric-acid ratio gives no information of either

metabolism, it is a dietary index solely. While a certain amount of purin may be converted into urea and a certain amount of urea may be utilized in the synthesis of uric acid, the amount of nitrogen concerned is too small to affect the total nitrogen, while the relations of these two processes to the purin total are not known. The purin metabolism is, however, not entirely independent of the general metabolism, since a luxurious non-purin diet will reduce (that is spare) the purin output to a slight extent. In starvation the purin output is not reduced corresponding to the reduction in the urea. The nucleinic metabolism is an integral part of the daily life of the cellular nuclei; it is not notably reduced in starvation or replaceable by any other metabolism, and has no role in the caloric or energetic aspect of general metabolism. In general language we may say that the cells that elaborate protein, sugar, and fat, for the purposes of the general metabolism, wear out in these efforts a certain amount of nuclein in their own internal mechanisms.

Exceedingly important are the questions that relate to the form in which the uric acid circulates in the blood, its solubility, and the influence of the reaction of the blood upon these relations. We do not know in what form uric acid and the bases circulate in the blood. This is a physico-chemical problem and it has never been investigated as such with proper methods. It is difficult to understand how, in a complex fluid like the blood, containing electrolytes, colloids, and many amphoteric substances and practically saturated with a gas of acid reaction, a substance like uric acid, which contains no carboxyl groups and has an extremely low co-efficient of solubility and constant of dissociation, should be combined with a cation like sodium to form an electrolyte. It is quite certain that uric acid cannot circulate to any extent in the form of the di-sodium urate (a pronouncedly alkaline salt) or of the mono-sodium urate (a feebly alkaline salt); the so-called hemi-urate is a fiction. Facts that have been demonstrated in researches on the purins point to a different conception. It has been long known that no known method of direct precipitation will throw down all the uric acid and purin bases in an extract of a tissue or in blood. It is now known that some of the pyrimidin derivatives of nuclein combine to form with uric acid complexes that do not give the ion reactions of uric acid and are not precipitable by the metallic salts, and of these substances one, thymic acid, has been identified. It is most natural to consider whether it may not be in some such form that uric acid circulates. Blood serum will dissolve forty times as much uric acid as distilled water (1 to 1,000 as against 1 to 40,000). This uric acid does not yield the ion reactions of uric acid, and can be recovered only after boiling with an acid; obviously some complex combination needs to be split by hydrolysis. The fact that uric acid will crystallize out from the blood serum about a suspended thread is not a proof that the serum is saturated. It has been shown experimentally that such a serum will dissolve more uric acid.

Analyses of uric acid in the blood are approximate only. Abnormal amounts have been determined to exist in most cases of acute gout, in many cases of nephritis, arteriosclerosis, pneumonia in the stage of resorption, in conditions associated with the disintegration of cellular exudates, following a meal rich in nuclein, and most markedly in leukæmia. Whenever an increased blood-content is accompanied by an increased output, it may be reasonably inferred that an exaggerated nuclein metabo-

lism or purin input exists. Whenever an increased content is not accompanied by an increased output, as in gout and nephritis, there remain two possibilities,—if one assumes that the chemical form in which the uric acid circulates is the same as in the normal,—a decreased oxidation of uric acid or a retention through failure of renal elimination.

As regards gout, there is no evidence that the gouty individual displays any abnormality in the assimilation of purin; the ingested purin is quantitatively absorbed from the digestive tract, as shown by the nitrogen balance and by the elimination of phosphoric acid. In some diet experiments the elimination of purin following the ingestion of sweetbreads was normal; in others there seemed to be a retention, the phosphoric acid was eliminated but not the purin. Whether such a failure could indicate a lack of oxygenation or a retention cannot be now decided. We need to know in detail how the gouty react in a quantitative and qualitative manner to variations in the purin input. The once current notion that gout is the direct result of an excessive purin input is devoid of any experimental basis.

Does the uric acid in the blood in gout circulate in the same form as normally? This has been denied by those who would explain the excess in the blood without resting it upon a simple retention. We have no data tending to show that the solubility of uric acid in the blood is decreased in gout. The hypothesis of the dependence of this solubility on the phosphates is a vague speculation. There is some evidence that the uric acid in the blood in leukæmia circulates in part in a form different from the normal.

Is there a diminished power of elimination of uric acid *per se* in gout? When we recall that from the purin output alone, even with a controlled purin input, the magnitude of the nuclein metabolism cannot be estimated, we realize that a retention cannot be thus determined. Conceding that many cases of gout have renal lesions and that many cases of renal sclerosis have urate depositions, it is still not possible to maintain that the excess of uric acid in the blood is the simple result of retention due to renal disease. The fact that the gouty kidney can eliminate an excess of uric acid after the ingestion of thymus, argues neither for nor against the theory, since a diseased organ may respond to extraordinary stimuli. On the contrary, the fact that in chronic nephritis the ingestion of thymus is followed by an increase in the blood-content as well as in the elimination, does not prove that the fault lies in the kidney. The renal theory of gout can be assumed only by postulating an elective type of purin nephritis. In chronic gout and in the intervals between the attacks in acute cases, the purin output is normal. Prior to the onset of an acute attack of gout there is a diminution in the uric-acid output, followed by an increase; it has not been shown that this bears constant relations to variations in the blood-content of uric acid. It is scarcely possible to believe that the attack is dependent upon the diminution in the output; the quantities concerned are too small to be the direct etiological factor. The depositions cut no figure in the quantitative relation; whether the urate depositions are ever absorbed with such rapidity and to such an extent as to show in the output is doubtful. Resolution in acute cases seems an act of phagocytosis rather than of solution.

The deposition of urates is not the direct result of an excess of uric acid in the blood; they are absent in conditions other than gout, particularly

leukæmia, in which an excess is present in the blood, and occur most often in chronic gout in which there is no evidence that the uric acid in the blood is increased. Nor is the deposition to be explained by the coincidental occurrence of an excess of uric acid in the blood and a lesion in the tissues. Gout would be very easy of experimental production if nothing but an excess of uric acid in the blood and a local lesion were required. The formation of tophi must rest upon some physico-chemical basis of precipitation and crystallization. That necrosis cannot be the sole substratum is certain.

These various facts compel us to assume that the actual etiology lies deeper than quantitative variations in the uric acid; the determining moment lies earlier in the purin metabolism. That these earlier factors may have relations to retention is not denied, but the retention is a result and not in itself an etiological factor. In a certain sense, the uric acid must be considered as the innocent weapon of the disease. The idea that the uric acid is itself the toxic agent, that it by a local action as uric acid inaugurates the local lesion, or that the local lesion is simply the reaction of the tissue to a crystallization of uric acid as a physico-chemical fact is contrary to our best knowledge. That the purin bases are devoid of that marked toxicity that was some time ago ascribed to them is now known; they are not in gout increased at the expense of the uric acid.

The hypotheses concerning the morbid physiology of gout most in harmony with our chemical and experimental data are two: Gout is a disease of the intermediary purin metabolism; gout is an auto-intoxication. The first may be formulated in several ways. It may be assumed that products are elaborated in the purin metabolism which cause local inflammations. It may be assumed that the uric acid normally circulates in combination in some pyrimidin complex, very soluble and easy of elimination, possibly by virtue of some dissociation in the kidneys; in gout this combination would be lacking or so altered that the uric acid would circulate in a form more resistant to excretion. Such alterations as are postulated in this theory may be demonstrated. Substances exist, as formaldehyde, that will pair with purins and thus protect them from further oxidation. Thymic acid combines with uric acid to form a large and stable complex which has totally different chemical relations than uric acid.

The disturbance could be localized either in the processes of assimilation of ingested nucleins or in the cellular purin metabolism. It is conceivable that the oxidation of the absorbed purin bases might be altered and their utilization in the synthesis of nuclein might be abnormal. This would reduce gout to a disturbance within the realm of the purin input. This is unlikely, since practically all of the known disturbances of metabolism have been shown to reside in the intermediary metabolism, not in the processes of digestion and assimilation. It may be assumed that the disturbance in the purin metabolism postulated for gout is resident in the cellular nucleinic metabolism.

The most recent theory rests upon the assumption that the formation of uric acid by oxidation of the nucleinic purin is more or less lowered and that instead, uric acid is formed by synthesis. Since, under these circumstances, the thymic acid with which the uric acid is held to circulate would not be available, the uric acid would circulate in a less soluble and elimin-

able and more easily precipitable form. The abnormality in the purin metabolism would thus be a sort of retardation; the mechanism whereby the synthetic formation of uric acid would be increased is entirely obscure.

The hypothesis that gout is an auto-intoxication other than in the purin metabolism is derived more from generalization than from research. It is conceivable that gout may be associated with disturbances in the common protein metabolism. It has been established that there is during the acute attack of gout a nitrogen deficit that cannot be explained by any possible deviation in the purin metabolism, and suggests a toxic exaggeration of the protein catabolism. Between attacks a nitrogen retention is often observed which may represent simply the recovery of protein lost during the attack or a retention of the end-products of protein catabolism. Gastro-intestinal auto-intoxication might be supposed to produce deviations in the assimilation of ingested purin, local lesions favorable to the deposition of uric acid, and also conditions in the circulation unfavorable to solution and excretion. It is obvious that in the end any theory of auto-intoxication extraneous to the purin metabolism becomes merged into the theory of deviations in the intermediary metabolism, and since data are as yet entirely wanting, it is more logical to presume that the primary disturbance lies not without but within the purin metabolism.

Oxaluria.—Oxaluria has been quite generally considered to hold some relation to the purin metabolism. There is no relation between the amount of oxalic acid in the urine and the quantity of crystals of calcium oxalate in the urinary sediment. Oxalic acid is formed in the normal body in the entire absence of the acid from the diet. Of the oxalic acid contained in the diet the larger part is destroyed in the alimentary tract. In all probability oxalic acid is not oxidized in the body. Oxaluria is no more common in the gouty than in others, and there is no clinical evidence of any relationship between oxaluria and disturbances of the purin metabolism.

In so far as the common protein metabolism is concerned, oxalic acid is formed from gelatine and kreatin; it is experimentally not to be derived from any excess of fat or carbohydrate in the diet. There is no experimental evidence that it is, in the body, derived from glycuronic acid or bears any relations to it. Oxalic acid is likewise easily obtained from the higher fatty acids, but there is no evidence that it is in any way associated with the normal fat metabolism or the abnormal acetone acidosis. Lastly, oxalic acid might be derived from the oxidation of oxy-acids such as lactic acid. In this manner it might be derived from sugar.

It is apparent that these facts shed no light upon the symptom-complex of oxaluria. That this symptom-complex possesses anything but a definite objective character is freely admitted. In any event there is no reason to incriminate the oxalic acid. In the quantities concerned it is innocuous and the symptoms currently attributed to the condition bear no resemblance to oxalic acid poisoning. That calculi form is a chemical accident. The most that may be claimed would be that the elimination of an excess of oxalic acid accompanies a symptom-complex, and may be assumed to indicate an underlying disturbance in metabolism. In which metabolism the assumed abnormality lies is not conjecturable.

AUTO-INTOXICATION ASSOCIATED WITH THE CARBOHYDRATE METABOLISM.

The digestion of the starches and the higher sugars is an act of hydrolysis. Ordinarily all the sugar absorbed (apart from pentoses) is in the form of hexose. It is possible under normal circumstances for higher sugars to be absorbed unchanged; the power of the alimentary tract to invert disaccharides is limited; beyond a certain point the sugar is absorbed unchanged. This mellituria is a strictly alimentary type; the sugar appears in the urine unchanged. In the common form of alimentary mellituria, the sugar in the urine is glucose, no matter what sugar was ingested. Normally no mellituria follows the ingestion of starch; time is the controlling factor in alimentary mellituria; if absorption be heavy in the unit of time, it will produce hyperglycemia. The normal individual will not exhibit mellituria following the ingestion of 5 ozs. (150 gms.) of glucose or levulose or nearly double that amount of saccharose or maltose; milk sugar is often less well tolerated.

The absorbed sugars are converted into glycogen but not all hexoses with equal readiness. Those sugars that undergo alcoholic fermentation, glucose and levulose, are easily converted; galactose slowly. The glycolytic fermentation takes place in the blood and general tissues, as well as in the liver, and the ferment and the conditions of its activity are the same throughout. It is not definitely known whether the different hexoses that are formed in the digestion of sugar (d-glucose, d-levulose and d-galactose) are absorbed unchanged or whether they are converted into d-glucose during the passage through the intestinal mucosa. In the event of their absorption unchanged they must be either converted into d-glucose in the liver or the liver must possess the faculty of forming glycogen from the different hexoses. According to our present evidence d-glucose is the combustion form of sugar; it is this hexose alone that is formed from glycogen, and the body unquestionably possesses the power directly, and probably indirectly, of converting the different hexoses into d-glucose. This is of practical importance, since it explains why the use of galactose or fructose is rarely of benefit to the diabetic; instead of burning the sugars directly, the body converts them into d-glucose. That the body can not only form d-glucose from d-galactose, but also form the latter from the former is shown by the synthesis of d-galactose in the central nervous system and in the breast glands.

Following the conversion of glycogen into glucose, the latter is utilized in combustion for the maintenance of the body temperature and the formation of fat. The reactions of the combustion of glucose are not definitely known. According to recent work, ferments that convert glucose into alcohol are present in all tissues; an intermediary stage in the reaction is lactic acid. Recent experimental work has made it probable that the combustion of sugar in the body follows in a general manner the following scheme: glucose→lactic acid→ethyl alcohol→acetic acid→methane→formic acid→carbon dioxide and water, carbon dioxide being set free also with the appearance of alcohol and methane, water being evolved with the appearance of acetic and formic acid. The particular importance of this scheme of oxidation lies in the fact that it makes ethyl alcohol a normal intermediary product in the sugar metab-

olism. The combustion of sugar is an act of fermentation. For the maximum acceleration of the reaction, substances derived from two sources are necessary,—the muscles and the pancreas. We may regard the muscular enzyme as primary, and the pancreatic substance (that seems to be associated with the integrity of the islands of Langerhans) as a zymo-excitor. It has not been proven that this relation is the sole one associated with the burning of sugar in the body, nor is the loss of the power of burning sugar always associated with lesions in the pancreas. Were this proven the problem of the intermediate carbohydrate metabolism would be greatly simplified. The process by which fats are formed out of sugar is not known. However this conversion is effected, the function is directly associated with the catabolic power of the carbohydrate metabolism, just as is the formation of glycogen.

Normally the body sugar is derived entirely from the carbohydrates of the diet. Many proteins contain preformed carbohydrate, which is available for the formation of glycogen; but the quantities are not large. It is, however, probable that when the sugar of the body is reduced, the body can secure it from other sources. For this purpose the protein and the fats are available and if they cover the caloric needs of the body little sugar need be derived at all. That an animal, fed on sugar free protein, may retain a little carbon while eliminating all the nitrogen is true, but this retention is slight and transient. Animals fed on a carbohydrate free diet may display a glycogen content that suggests a formation from the protein of the diet, but the figures are not conclusive. It is an error to assume that the facts and interpretations in diabetes may be applied to the normal individual, since sugar starvation and the inability to oxidize sugar are totally different things. While recent experimental work has made it quite certain that in the depancreatized dog, sugar can be formed from amido-acids derived from protein, it is an equally certain experimental fact that in the normal dog, sugar is formed only from carbohydrate.

No known disturbances follow the absence of carbohydrate from the diet. The use of carbohydrate alone (plus the necessary protein) to furnish the heat of the body seems equally harmless. When one recalls that the limit of assimilation of cane-sugar is some 200 grams, it is obvious that were an individual to supply his whole heat by the use of sugar, he would at each meal approach the limit of assimilation. This may be avoided by the substitution of starch for sugar and such a ration is adequate to the greatest physical exertion. If more carbohydrate be ingested than is necessary for the maintenance of the body heat, the remainder is converted into fat. The combustion of carbohydrate is determined not by the input but by the demands for heat and energy; to a small extent, however, the ingestion of an excess of carbohydrate may be followed by an increase in combustion, just as in the protein metabolism.

Important for the estimation of the carbohydrate metabolism is a reduction of the limit of assimilation. This may be lowered to less than one-half the normal with no signs of ill-health. This reduction is usually confined to glucose and saccharose, not to levulose and lactose. An alimentary mellituria associated with a starch diet is always pathological, indeed probably always diabetic. The best interpretation of the reduction of the limit of assimilation is that the power of the liver to convert a unit

of sugar into glycogen in the unit of time is reduced. Whether an absorption of sugar by the lacteal instead of the portal system accounts for alimentary glycosuria is not known. A lowering of the limit of assimilation is regularly seen in exophthalmic goitre and often in alcoholism, gout, arteriosclerosis, lead poisoning, organic diseases of the liver, obesity, and in some of the psychoses and organic diseases of the nervous system. A curious susceptibility to levulose has been observed in some cases of hepatic disease. The condition may be mild or pronounced and may be associated with a reduction in the power to burn sugar, but is in itself not associated with hyperglycæmia, apart from the period following the ingestion of the sugar.

Superoxidation.—An excessive combustion of sugar is a common phenomenon. Most prominent in Graves's disease, it is seen also in infectious diseases, in severe anæmia, in malignant neoplasms, and in cachexia due to other causes. It is usually not marked in the febrile infectious diseases; the supercombustion is less marked than the exaggeration of protein catabolism. Though such a superoxidation of sugar usually accompanies fever, it does not in itself need to produce fever. The excess of combustion has apparently two causes: an exaggeration in the fermentative acceleration and the lowering in the saving power of sugar for protein. The excessive combustion of sugar is in itself unattended with any untoward results, the body seems able to carry the process to the end-products of water and carbon dioxide; that the body may not be able to control the heat dissipation can be no fault of the carbohydrate metabolism.

Suboxidation.—A lessened combustion of sugar as a quantitative abnormality is, apart from acute conditions such as shock, hemorrhage, etc., probably met with only in true diabetes. In no other condition is there evidence that the body burns fat or protein to maintain the heat as the consequence of an inability to burn sugar. Since the combustion of sugar is a fermentation, the only dynamic explanation for the loss of the faculty, since the concentration of the sugar is not lowered, is to assume the loss of the ferment or of some zymo-excitor, or the presence of some condition in the system inimical to the action of the ferment.

Glycosuria.—Glycosuria may be associated with normal or hyperglycæmia. An increase of sugar in the blood may be due to an increased formation or a decreased oxidation. Glycosuria with a normal blood-content is probably associated with some abnormality in the renal functions. We have evidence that all these forms exist clinically. That of the number of non-diabetic glycosurias many are best explained as results of renal disturbances is certain. Glycosuria due to an increased formation of sugar may be due either to an excessive input, to an inability of the body to convert the absorbed sugar into glycogen, or to what might be termed an instability in the storage of glycogen. Sugar is known to circulate in complex combinations (possibly colloidal), in fact the least part of the circulating sugar exists in the simple state. It is pertinent to inquire whether abnormalities in these relations, independent of hyperglycæmia, might not lead to renal elimination. Glycosuria *per se* need have no consequence to the metabolism. While it is current teaching that hyperglycæmia *per se* exerts a deleterious action upon the tissues, many individuals have persistent glycosuria without signs of disturbance in the

carbohydrate or other metabolisms. It is, however, possible experimentally to show that cells are quite sensitive to higher concentrations of sugar.

Diabetes.—In diabetes are concerned several disturbances of intermediary metabolism: loss of the power of burning sugar; loss of the power in the liver of converting sugar into glycogen; loss of the power of converting sugar into fat; loss of the power of burning fat completely and in the normal manner; and a loss of the normal tendency to remain upon a minimum plane of carbohydrate metabolism when on a carbohydrate free diet. The ordinary distinction between diabetes and glycosuria,—the persistence of sugar in the urine (*i. e.*, hyperglycemia) following the withdrawal of carbohydrate from the diet—is convenient but pathologically inexact, since cases pass from one to the other side.

The loss of the function of oxidizing sugar is a gradient in which the successive lapses may be grouped about as follows, in the order of their severity: The loss of the power of assimilating starch—mellituria after starch ingestion; reduction in the limit of assimilation of sugar to the point when any sugar causes a glycosuria; reduction in the assimilation of starch to the point when any starch is followed by glycosuria; the partial loss of the power of burning sugar; the loss of the power of burning sugar during exercise; the loss of the power of burning more sugar during fever; the loss of the saving power of carbohydrates on the protein metabolism; and the total loss of all power of burning sugar. The last is extremely rare. The cases in which sugar no longer spares protein and supports in part fever and muscular exercise are uncommon. The succession of losses in function do not necessarily occur in the order given and a function once lost may be regained. In proportion to the loss in the power to burn sugar, the heat of the body must be maintained by the combustion of protein and fat in the diet or from the body. The inability to convert sugar into glycogen is rarely lost, the tissues are not devoid of glycogen. The power of prompt conversion of alimentary sugar is lost. The power of forming fats from sugar is reduced, in severe instances entirely absent.

The origin of the excessive glycemia is a fundamental problem in diabetes. It is now generally held that the quantities of sugar eliminated in severe diabetes on a carbohydrate free diet cannot be explained on the basis of the preformed glycogen and glycosides, or the preformed carbohydrate contained in protein. The sugar must be derived from the protein or the fat. Under fat is understood fatty acid; though glycerine can be converted into fat, the available quantity is too low to make it of moment. Within recent years the views with reference to the formation of sugar from protein have undergone a change. Formerly it was assumed that protein was separated into a nitrogenous and non-nitrogenous moiety; from the latter the glycogen was derived directly. Recent studies have shown that the end-products of protein catabolism are amido-acids, and that the carbon as well as the nitrogen of the protein is to be found in these products. Consequently, the formation of sugar from protein means the formation of sugar from amido-acids. The experimental formation of sugar from amido-acids is an open question. It must be pointed out that all the substances theoretically regarded as intermediary stages in the formation of sugar from amido-acids are fatty acids that could be easily

derived from the fats. The formation of sugar from protein in the diabetic body has been recently made probable by the study of the utilization of leucin and phenylalanine in the depancreatized dog.

The following facts speak for the formation of sugar from protein: The elimination of sugar in diabetes is often parallel to the protein catabolism; the ratio of glucose to nitrogen is often about 3 to 1 which corresponds to the relations in the molecule of protein. The ingestion of pure protein (as casein) is often followed by a proportional rise in the glycosuria; reduction of the protein in the diet will often lead to a diminution in the glycosuria. The glycosuria goes hand in hand with nitrogen deficit, if the protein in the diet be insufficient. When starved animals freed of glycogen by strychnine are infected with the colon bacillus, their bodies present more glycogen than the controls and this is held to have been derived from the products of excessive protein catabolism. The respiratory quotient in diabetes is low. In favor of the origin of the sugar from the fats are the following facts: In many of the worst instances of diabetes, especially experimental, the ratio of glucose to nitrogen is far higher than the ratio in protein, as high as 8 or 10 to 1; the sugar could not be derived from the protein except upon the assumption that a remarkable nitrogen retention has occurred. In many instances of ordinary diabetes the regular ratio speaks against a derivation of the sugar from the protein alone. The greatest glycosuria is often associated with the most marked excesses of fat combustion as revealed by the acidosis. The digestion of fatty acids with liver pulp yields sugar.

Against the origin from protein speaks the practical impossibility of showing experimentally that a healthy animal ever derives sugar from protein, but it is going too far to apply these results unreservedly to the diabetic. Directly opposed is the fact that when the fatty acids held to be intermediary between leucin and alanine (capronic and propionic acids) are administered to diabetics, they appear in the urine as acetone and not as sugar. Opposed to the origin of sugar from fat is the fact that one cannot increase the glycosuria by increasing the fat in the diet. The ingestion of lecithin does increase the glycosuria.

Some of these interpretations rest upon misconceptions of general metabolic relations. That the ingestion of protein may increase the glycosuria, while the ingestion of fat does not, cannot speak directly in favor of the origin of sugar from protein instead of fat, because the disintegration of protein within the body is proportional to the input while the combustion of fat is not proportional to or dependent upon the input. The ratio of nitrogen to sugar cannot be employed in favor of the origin of sugar from protein when the ratio is low, or the origin from fat when the ratio is high, because in neither case are we able to fix the relations of nitrogen input, retention, and output. The only proper standpoint is that the source of the excessive sugar in diabetes, whether from the protein or the fat, is undetermined. From theoretical relations, the origin of the sugar from fat would be the more simple, as we would have sugar derived normally from fat and representing the intermediary product of fat on the route to combustion; in diabetes the loss of the power of burning glucose with the continuation of the conversion of fat to sugar would account for the hyperglycæmia, leaving more or less entirely to the protein catabolism the heating of the body. On the other hand, since it seems

quite certain that normally sugar is not formed from protein, we need in the diabetic the postulation that accompanying the non-oxidation of sugar is an abnormal formation of sugar (that cannot be burned) from the intermediary products of protein metabolism—just the converse of a compensatory mechanism. The crucial experiment would be the demonstration that the diabetic man or dog during the course of the disease elaborates upon a protein diet more sugar than could be accounted for by the glycogen and other carbohydrates and the body fats; this experiment has been several times attempted in dogs, with negative results.

The gas-exchange is normal in diabetes, except in the attacks of coma, where it is probably subnormal. The carbonous metabolism is always unbalanced. The respiratory quotient is very low and is not raised by the ingestion of carbohydrate. With good powers of digestion it is usually possible to obtain a nitrogen balance, except in the periods of deterioration. It requires much more protein than normal to accomplish this and this greater amount of protein is directly proportional to the gravity of the case. For this condition, which is an important practical one, we have first the explanation that fat does not equal sugar in its power of sparing protein. But only in the mild cases is this explanation sufficient; a diabetic will commonly have a nitrogen deficit on a diet of fat and protein such as would fully suffice for a normal individual. Those who consider that in diabetes sugar is regularly formed from protein, explain this on the ground that the diabetic does not utilize the non-nitrogenous moiety of the protein consumed. Those who incline to the view that the diabetic forms sugar from fat explain the condition by the assumption that the body has lost in part the power of burning fats, of which the acetone acidosis is an evidence, and this leaves a deficit that must be made good by the utilization of more protein. In attacks of diabetic coma the nitrogen deficit is most marked, so marked in fact that an additional explanation is usually sought in a toxic exaggeration of the protein catabolism.

To what the toxic symptoms of diabetes are due is known only in part. In all probability the intoxications come rather from the perverted protein and fat metabolism than from the suboxidation of sugar. The coma is an acidosis, due to the perversion of the fat catabolism. While there is no direct evidence that hyperglycemia *per se* exerts a toxic action, the fact remains that the general condition of the diabetic is made worse and his power of burning sugar still further reduced by the ingestion of carbohydrate, while the maintenance of a strict diet will ameliorate the symptoms and tend to a recovery of the power of burning sugar. Some of the toxic symptoms, as the disturbances in nutrition of tissues, are not related to the acidosis, the toxicity of the acetone bodies or to the hyperglycemia, but seem to rest upon some deeper abnormality in the protein metabolism.

The investigations on diabetes teach another lesson. We hear so much of suboxidation, it seems as though it were supposed that the body would suffer such a condition without any attempt at a regulation. Now all these alterations in the protein and fat metabolism in diabetes are in a general sense simply the regulatory mechanism that prevents a suboxidation. There is a great leeway in the direction of increase in the physical dissipation of heat, there is much less in the direction of reduction. When one main combustion is cut out, practically the full normal function

of heat production is thrown upon some other metabolism. There is no evidence that the diabetic attempts to minimize the results of the loss of the power of burning sugar by restricting the dissipation of heat as the myxœdematous seem to do. Yet this would be directly the most saving act the body could attempt.

AUTO-INTOXICATION ASSOCIATED WITH THE FAT METABOLISM.

The digestion of fat is an act of simple hydrolysis, the fats being split into the fatty acids and glycerine. Fat is carried in the circulation partly in emulsion, favored by the colloidal nature of the blood plasma, but largely in solution. The fat in solution in the blood is dialyzable and apparently enters the cells in that form, there to be in part reconverted into insoluble fat. Since it is easier to picture chemical reactions in a homogeneous rather than in a heterogeneous system, we may assume that the fat is utilized in the metabolism in this soluble state of unknown nature. The process of formation of fat from sugar is not known; it seems likely that it is formed indirectly from fatty acids derived from the partial oxidation of sugar. The seat of the conversion is also unknown, though the liver is credited with the function. That fat is normally formed from protein is very unlikely. Fat is the most potential form of carbonous food and is able to supply the entire caloric demands of the body. Nevertheless fats do not equal carbohydrates in the power of saving protein.

The reaction of the combustion of fat is not known. A direct combustion could occur, successive CH_2 groups being split off and burned. It is, however, a question whether a different procedure be not the true one. A trace of acetone is present in normal urine, derived from the reduction of diacetic acid. Whenever the fat catabolism is exaggerated, the acetone is increased and diacetic and β -oxybutyric acids may appear. We do not know whether these substances are normal intermediary products in the fat combustion or products of an abnormal reaction of oxidation. If the acetone group represents an abnormal qualitative variation, it could be compared to cystin in the purin metabolism; if an intermediary product, it may be compared to leucin and tyrosin. Acetone itself is not oxidized in the body. It is derived from aceto-acetic acid by reduction, carbon dioxide being split off. The diacetic acid is derived from β -oxybutyric acid by oxidation. If these acids are normal products in the oxidation of fats, the reduction of diacetic acid to acetone is an abnormal reaction. Nevertheless, the normal trace of acetone is increased in every condition accompanied by an exaggeration in the combustion of fat. Normally β -oxybutyric and diacetic acids, when ingested, are oxidized, no appreciable reduction of the diacetic acid to acetone occurs. It is known that the normal body could not oxidize the quantities of these acids that are to be met with in the diabetic. If the combustion of fats proceeded directly these oxy-acids would not be formed. There is some evidence that normally the body does not oxidize butyric acid to oxy-butyric acid, but instead splits it into two molecules of acetic acid and burns these directly. Since the normal urine contains a trace of acetone, it is apparent that we have here a condition common enough in the domain of organic reactions,

where a major reaction is accompanied by a minor side reaction. In the state of the acetone complex, something converts the side reaction into the main reaction in the quantitative sense.

Suboxidation.—Of a suboxidation of fat we have no knowledge. There is no call for any oxidation of body-fat so long as the sugar and protein of the diet are sufficient to the caloric needs of the body. When the calories of the diet are presented partly in the form of fat, the diet-fat and not the body-fat is utilized.

Superoxidation.—A superoxidation of fat occurs under all circumstances associated with a superoxidation of sugar if the sugar of the diet be insufficient. Except in Graves's disease and rapidly advancing malignant neoplasms, it is usually possible, if the powers of digestion are normal, to administer such an amount of sugar and fat as to leave the body-fat intact. The greatest exaggeration of the fat catabolism is seen in diabetes. Here it is always associated with an excessive utilization of protein from the diet or body. It is often impossible in a diabetic by the administration of fat to hold the catabolism to the level of the normal. More fat is furthermore utilized than is apparent in the respiratory exchange.

Superoxidation of fat is always associated with the appearance of the acetone bodies in the urine. This supports the theory that these acids are normal intermediary products in the fat catabolism. Their appearance indicates either some limit to their oxidation or an abnormality in the last stages of the reactions. The interpretation of this would obviously be totally different, depending on whether one considers that the fats are burned as such or converted into sugar. The formation of the acetone substances bears no known constant relation to the total combustion of fat; apparently it represents but a small fraction, the larger part proceeding to the natural end-products. In grave terminal diabetic coma, however, but little of the fat combustion reaches the final stage; it seems largely diverted in the acetone direction (1 mol. fat—4 mol. β -oxybutyric acid). This of course does not furnish much heat, and is one reason why the protein catabolism is so exaggerated in these comas, since it is then the only metabolism that can furnish heat for the body.

The Acetone Complex.—Under this term we group the associated elimination of acetone, diacetic acid, and β -oxybutyric acids in the urine. The term acetone complex is coined to differentiate the condition from the acidosis due to other acids. Except in the last stages of diabetic coma, the acids circulate and are eliminated as salts. The acetone bodies are derived from the fats and not from the carbohydrates or protein. Perfusion of the liver with phenyl-amido-acids will yield acetone, and there is no bar chemically to its derivation from lactic acid. Clinically, in all the different groups of the acetone complex, when the condition is severe the acids accompany the acetone, and this speaks directly against the origin of the acetone from the protein catabolism in these cases.

The current conception of the acetone complex connects with it disturbances in the carbohydrate metabolism in the sense that a cessation of the carbohydrate metabolism comprises the essential condition for the elimination of acetone, diacetic, and β -oxybutyric acids, the oxidation of the higher fatty acids to carbon dioxide and water being only then completed, when a certain amount of carbohydrate is simultaneously burned.

There are instances of acetonuria in which this does not hold, and in which there are many things tending to prove the contrary. In phloridzin diabetes the acetone complex does not appear so long as the animals are in nitrogen balance, but appears with the installation of a nitrogen deficit. If a phloridzin dog be starved, the acetonuria disappears with the glycosuria. There are instances of the acetone complex in which there are no signs to indicate any disturbance in the carbohydrate metabolism, or indeed any exaggeration in fat combustion. Cases occur in which we have no evidence that the protein, carbohydrate or fat metabolism exhibit any quantitative variations, and only the fat metabolism displays this qualitative variation. Acidosis from any cause is very easily developed in childhood and often to an exaggerated degree under even trivial illness. The origin of the acetone complex in diabetes would be simplified if we believed in the normal conversion of fats into sugar; an interruption in the combustion of the sugar would necessarily entrain a disturbance in the intermediary fat metabolism.

Acetone Complex Associated with a Low Carbohydrate Combustion.—**Starvation.**—A few days after the withdrawal of food, the acetone group appears in the urine. When the stored glycogen is burned up, the heat must be derived from protein and fat, and since the nitrogen output is restricted, the bulk of the heating falls to the burning of the fats. It persists so long as the starvation continues. A pure protein diet or a protein-fat diet has the same result.

In *febrile diseases* the complex is common. The fever makes large demands on the carbohydrate metabolism, the hepatic glycogen disappears, and, as the input is under these circumstances usually diminished, an exaggerated burden falls on the combustion of fats. β -oxybutyric acid is rare in the febrile acetonuria; diacetic acid is often present. In *diabetes* the body seems to have lost in large part the normal power of burning diacetic and β -oxybutyric acids. In diabetes, as in the two previous conditions, the administration of sugar will lower the output of the acetone substances. In severe cases the administration of sugar will not lower the output of the acetone substances, but this may be done by the administration of alcohol or glycuronic acid.

Instances of Acetone Complex in which there is no Evidence that the Carbohydrate Metabolism is Deranged.—In the cachexia of carcinoma, in severe infections, in atrophy of the gastric mucosa, in severe cases of anæmia accompanied by a rapid loss of flesh, we may encounter the acetone complex. It is rarely marked, β -oxybutyric acid is usually absent while diacetic acid is not always present. In these cases the individuals are ingesting carbohydrate, there is no mellituria, there are no signs that the carbohydrate metabolism is exaggerated or depressed, there is nothing to indicate that there is in the body either a diminution of the glycogen or a loss of the power to convert it into sugar, to burn sugar, or convert it into fat. In this group the fat catabolism is abnormally increased, body fat is being burned.

Instances of the Acetone Complex without Quantitative Alterations in Any Metabolism, with Normal Qualitative Protein and Carbohydrate Metabolism.—Here are to be classed those seizures associated with marked gastro-intestinal symptoms. The subjects are usually in good health, the onset is sudden, the symptoms of irritation of the alimentary

tract are marked. There is pronounced urinary acidosis; grave nervous symptoms may supervene, even death. Most of them yield promptly on lavage of the stomach and colon, free purgation, and symptomatic treatment. Many resemble exactly toxic gastro-enteritis but others are obviously something more. Fatal cases have been reported. Here also must be grouped the cases of recurrent vomiting in children associated with this complex. There are in these no symptoms of gastro-intestinal lesion; the vomiting is reflex in all likelihood. Probably related are the cases of convulsive pseudo-epileptic seizures associated with acetonuria. These subjects are all on ordinary mixed diet, have no glycosuria or albuminuria, and usually recover under symptomatic treatment. The administration of sugar does not affect the acetonuria. That they are ever of gastro-intestinal origin, in the sense that the acetone bodies are formed in the alimentary tract and then absorbed, is entirely without evidence; it has never been shown that these substances can be formed by any abnormality of fat digestion or bacterial fermentation. The only logical explanation, if one inclines to a gastro-intestinal etiology, is to assume that a hypothetical gastro-intestinal auto-intoxication inaugurates secondarily a perversion of the intermediary fat metabolism.

In this connection the writer can report a controlled experimental observation. A healthy man was placed on an ash-free diet composed of washed egg albumin (75 gm.), olive oil (120 gm.) and cane-sugar (250 gm.). A nitrogen balance was promptly established; the urine was in every way normal. On the seventh day, following the onset of prodromal nervous symptoms, a marked elimination of acetone and diacetic acid set in, following which the experiment was discontinued. The complex disappeared within a few hours after the ingestion of salt. No weight was lost. Here, therefore, the acetone complex was the result of withdrawal of salts and cations, of an acid intoxication. There is no reason to suppose that there was any qualitative or quantitative abnormality in either the protein or carbohydrate metabolism or any exaggeration in the fat combustion. A person on a normal diet of protein, in nitrogen balance, on 250 gm. of sugar and free from glycosuria, cannot be considered to have any abnormality in those metabolisms upon which to rest an association with the acetone complex.

Instances of Acetone Complex Associated with Disturbances in the Protein Metabolism.—There are now quite a number of cases reported in which following anæsthesia the patients suddenly pass into a state of intoxication, often with jaundice, acetone acidosis, the elimination of leucin and tyrosin in the urine, coma and death, with the finding of extensive degeneration of the liver at autopsy. In many cases following operations, particularly in children, a transient acetonuria occurs without dangerous symptoms. These cases present no signs of abnormality in the carbohydrate metabolism. Hemorrhage into the large body cavities seems to be followed by acetonuria.

An interesting group of conditions in which the acetone complex may occur is seen in diverse exogenous intoxications with phosphorus, phloridzin, etc. It is not possible to believe in advance that these poisons act alike in this regard, nor can it be urged that they bring about a cessation or reduction of the carbohydrate metabolism. Very interesting is the acetonuria commonly seen on withdrawing morphine from an habitué;

if the drug be resumed the complex disappears. The logical interpretation is that the deviation in the fat combustion resulting in the acetone complex may be brought about by several causes. How these operate to disturb the intermediary fat metabolism is unknown; but that many cases exist in which the phenomenon cannot be explained as associated with any known abnormality in the carbohydrate metabolism must be obvious.

Mode of Action of Intoxication in the Acetone Complex.—The mode of intoxication may be referable to the substances themselves or to their behavior as acids. The term acidosis expresses the view that in their behavior as acids lies the chief harm. Acetone is but slightly toxic. The salts of diacetic and β -oxybutyric acid have some toxicity, which is probably greater in the diabetic because of the inability to oxidize them. When one considers the really enormous quantities of the substances that may be voided in a day, one must hesitate to say that there can be no direct intoxication from them. The general interpretation is that these acids act by withdrawal of cations. How this leads to a secondary intoxication is not known, but it does so in experimental acid intoxication. That the acids circulate as such cannot be true, except during the closing hours of life. The carbon dioxide of the blood in diabetic coma has been found reduced to less than one-half the normal. This cannot be necessarily attributed to any alteration in the reaction of the blood and it is probably the result of moribund suboxidation. The sudden onset of symptoms in the acute cases can scarcely be explained on the ground of simple acidosis, yet alkali treatment is here most effective. It is a noteworthy fact that the injection of sodium bicarbonate is followed as a rule by recovery in the non-diabetic cases, as an exception in diabetes—although this does not in itself antagonize the contention that the intoxication is simply an acidosis.

It is possible that an acidosis may be brought about by the reversed process: not by formation of organic fatty acids with secondary withdrawal of ammonia from the urea metabolism, but by the non-functionation of the urea metabolism, whereby large amounts of ammonia are not utilized and thus bind fatty acids that would otherwise have been oxidized. In some severe hepatic diseases, unassociated with disturbances in the carbonous metabolism, acidosis appears and the attempt has been made to refer it to the abolition of the hepatic functions.

PART V.

DISEASES DUE TO VEGETABLE PARASITES OTHER THAN BACTERIA.

By JAMES HOMER WRIGHT, A. M., M. D., Hon. S. D. (HARV.)

In this section are considered certain general and local diseases due to infection with fungi and certain branching filamentous microorganisms which are classed by some writers also among the fungi, but which may be regarded as representing intermediate forms between the bacteria and the fungi. Various local fungus diseases of the skin, such as favus, pityriasis versicolor, and erythrasma, known collectively as the dermatomycoses, are not included.

Concerning the relationship and classification of the parasitic and pathogenic fungi, there is much uncertainty and lack of agreement among authorities. The subject has been thoroughly covered by Plaut,¹ Busse,² and Ricketts.³

The theory of the etiological relationship of yeast-like fungi, or so-called blastomycetes, to malignant tumors now requires no further consideration than the statement that the results of all the most trustworthy work of the past few years have brought nothing in the support of the theory but have tended thoroughly to discredit it.

CHAPTER XV.

ACTINOMYCOSIS.

ACTINOMYCOSIS is a suppurative process combined with growth of connective tissue and characterized by the presence in the lesions of vegetations or colonies of a specific microorganism, *Actinomyces bovis*. The disease may be local or general, subacute or chronic. It should be distinguished from so-called pseudotuberculosis or *Streptothrix* or *Cladothrix* infections or atypical actinomycosis. Such processes are considered in Chapter XVI, under the name of Nocardiosis.

Actinomycosis affects man and certain mammals, particularly cattle, in which it has been called "lump jaw," or "big jaw." The disease has

¹ *Handb. d. Path. Mikroorganismen.* Kolle u. Wassermann, 1903, I, 526.

² *Handb. d. Path. Mikroorganismen.* Kolle u. Wassermann, 1903, I, 661.

³ *Journal of Medical Research*, 1901, VI.

a wide geographical distribution and is probably much more common in man than is generally recognized. According to Erving,¹ one hundred cases in man had been observed in America up to December, 1901.

In cattle, bovine actinomycosis had long been known chiefly as a form of sarcoma of the jaw, when Bollinger, in 1877, first clearly showed that the disease was due to infection with a vegetable parasite, to which Harz gave the name of *Actinomyces bovis* on account of the radiate structure of its colonies or vegetations in the tissues. Shortly after this, J. Israel described cases in man, which we now know to be actinomycosis, and also described the characteristic microorganism, which he regarded as the infectious agent, but he did not recognize its identity with the microorganism described by Bollinger. The identity of the human and bovine disease was first pointed out by Ponfik.²

Etiology.—The specific infectious agent exists in the lesions and in the pus in the form of small whitish, or yellowish, irregular shaped granules varying in diameter from a fraction of a mm. to 1 or 2 mm. Larger granules are usually made up of aggregations of smaller ones so that they present a mulberry-shape. The granules may be soft and easily crushed or hard, resistant, and even calcareous. The essential element of the granules is a branching filamentous microorganism and certain transformation and degeneration products thereof. Typically the granules present the following peculiarities of structure under the microscope. Over more or less of the periphery of the granule, are closely set, hyaline, refringent, club-shaped bodies of varying size and thickness arranged in a radiate manner, while elsewhere the periphery is occupied by filaments of the microorganism likewise closely set together and disposed in a radiate manner. All transitions between the filaments and the club-shaped bodies may be present. Beneath this peripheral layer of radiating club-shaped bodies and filaments is a dense network of branching interlacing filaments, while the central part of the granule may be occupied by necrotic and degenerate filaments and pus cells. The club-shaped bodies develop out of the peripheral filaments by the latter becoming invested with a sheath of hyaline refringent material which is usually thickest at or near the distal extremity of the filaments, and thus club-shaped bodies with filaments in the centre are produced. The "clubs" may attain a thickness many times that of the filaments, which may degenerate and disappear from within them. This sheath formation may extend to the deeper lying filaments in the granule and these, likewise, may degenerate and become invisible so that the granule may finally be transformed into a mass of hyaline refringent substance and necrotic material, invested at the periphery with closely set radiating club-shaped bodies but without a trace of the filamentous microorganism out of which it was originally formed. In the "clubs," degenerate changes may occur whereby they acquire a lamellated structure or assume a variety of shapes and appearances. Eventually the granule may be absorbed or become calcified.

The "clubs," or rays, are usually better developed in the granules in bovine lesions than in human lesions. In the latter they may be absent or poorly developed and the granules may consist entirely or chiefly of filaments. Certain cases in which the granules were destitute of "clubs"

¹ *Bulletin of the Johns Hopkins Hospital*, 1902, XIII, 261.

² *Berlin Klin., Wochenschr.*, 1879, 345.

have been erroneously regarded as not cases of genuine actinomycosis and have been called pseudo-actinomycosis. This name has also been applied to certain suppurative conditions in which masses of various bacteria have been observed.

Harz¹ regarded the "clubs" as organs of fructification, and Bostroem² and others regarded them as degeneration products of the microorganism.

In general, the club formation is most marked in lesions in which there is considerable development of connective tissue and in which the progress of the disease is slow, with manifest resistance on the part of the tissue to the spread of the process; while in relatively rapidly progressive cases or those in which there is little evidence of resistance on the part of the tissue to the infection, "clubs" may be wanting on the granules. The writer³ has shown that blood serum and serous pleuritic fluids are capable of provoking club formation by filaments in artificial growths of the microorganism that had been immersed in these fluids. From these facts and observations it seems probable that the club formation is a protective device, adopted by the microorganism to protect for a time the main mass of the microorganism constituting the granule from the destructive action of the tissue cells and juices.

Concerning the biology of the specific microorganism of actinomycosis, much confusion has existed for a long time and much that is erroneous has been written. Many workers have made culture experiments with the microorganism with very varying and often contradictory results. The subject has been further confused by classing with actinomycosis certain other suppurative processes due to infection with branching microorganisms which are widely different from the specific microorganism of actinomycosis, and should be called *Nocardia*.

The various branching microorganisms claimed to have been isolated in cultures from actinomycotic lesions, and to represent the microorganism of the lesions, may be roughly divided into two groups. All of these at some stage in their developmental cycle occur in filamentous forms, without sheaths or septa, and of a thickness of a medium sized bacillus. They are distinguished from the bacteria by their peculiarity of truly branching, and may be regarded as occupying a position in the botanical kingdom between the bacteria, on the one hand, and the hyphomycetes or mould fungi, on the other. One group is represented by the microorganisms described by Bostroem,⁴ and a few others; the other group, by the microorganisms of Wolff and Israel,⁵ the writer,⁶ and many others.

The first mentioned group grow readily on all culture media, both at the room temperature and in the incubator. Their chief characteristic is the formation in cultures of spherical, spore-like, reproductive elements out of the substance of their filaments. None of this group are known to be capable of producing in animals inoculated with them, lesions like actinomycosis and containing the characteristic granules.

¹ *Jahresber. Thierarzneischule. München*, 1877-1878; *Deutsch Zeitschr. Thiermed.*, 1879, V, Suppl. heft., 125.

² *Beitr. Path. Anat. u. allgem. Path.*, 1891, IX, 1.

³ "The Biology of the Microorganism of Actinomycosis," The Samuel D. Gross Prize Essay, *Journal of Medical Research*, 1905, XIII, 349.

⁴ *Beitr. z. Path. Anat. u. z. Allgem. Path.*, 1891, IX, 1.

⁵ *Virchow. Arch.*, 1891, CXXVI, II.

⁶ *Loc. Cit.*

The members of the other group do not grow on all the usual culture media and only feebly or not at all at room temperature. They do not form spore-like reproductive elements. Some of them have been shown to produce in animals inoculated with them, lesions essentially identical with those of typical actinomycosis although not of a progressive character.

The subject of the biology of the microorganism of actinomycosis has recently been discussed by the writer, who concludes, from his own culture experiments and the analysis of the work of many others, that only one species of microorganism, *Actinomyces bovis*, represents the specific infectious agent of true actinomycosis in man and animals.

This microorganism has properties essentially like those of the second group above mentioned. The microorganisms of the first group, described by Bostroem and others, should not be considered as representing the microorganisms in the lesions, but are to be regarded as secondary invaders of the lesions or extraneous microorganisms accidentally infecting the cultures.

Concerning the mode of entrance of actinomyces into the tissues, it is generally taught and believed that this microorganism is widely distributed in the outer world on grains and vegetable material and that it is carried into the tissues by penetrating foreign bodies of this kind, upon which it has its normal habitat. This idea is based on the following considerations:

The frequent occurrence of such foreign bodies in actinomycotic lesions; a history, in many cases, of the patient having taken uncooked grains or other vegetable material into the mouth; the occurrence of pulmonary actinomycosis in those who have breathed the dust of dried grains; the occurrence in the outer world, upon grains and grasses, of microorganisms with biological characters similar to, or identical with, those of the first group above mentioned—which Bostroem, Gasperini and others claim to have isolated from actinomycotic lesions; the almost exclusive origin of actinomycotic lesions in the tissues and structures associated with the respiratory or alimentary tracts.

This widely accepted idea is erroneous, because *Actinomyces bovis* does not have the biological characters of this saprophytic group assigned to it by Bostroem and a few others whose culture work is open to doubt, but has biological characters which would suggest that it does not have its normal habitat outside the body. The specific microorganism of actinomycosis probably exists normally among the abundant flora of the secretions of the alimentary tract, where it has not been recognized because it exists there in a form which is not characteristic and very unlike that which it assumes in the lesions; it may gain entrance to the tissues through wounds, made by penetrating foreign bodies or otherwise, or through lesions due to carious teeth, or may invade the lungs as do other bacteria of the mouth and pharynx; in the tissues, under certain conditions it develops into the characteristic colonies or granules and by further proliferation gives rise to the disease. The disease in and about the jaw is frequently associated with carious teeth.

Besides the specific and characteristic microorganism, various bacteria are also present in the lesions in many, if not most, cases of actinomycosis, and it seems very probable that these play an important part in the production of the disease in these cases.

Contagiousness has not been shown for actinomycosis. The small amount of evidence tending to show that it is contagious will not stand critical examination and there is much direct evidence that it is not.

Many experimenters have attempted to reproduce the disease by inoculating animals with material from actinomycotic lesions, but the results of most of them have been negative or ambiguous. Only a few report results that apparently constitute a true reproduction of the disease. In view of the low degree of virulence thus manifested by *Actinomyces bovis* in healthy experimental animals, it would seem that the occurrence of the natural disease must be due in large measure to the existence of an individual susceptibility to the infection. Thus it is most frequent in individuals living under unfavorable hygienic conditions. Infection from drinking milk and eating the flesh of diseased animals has never been proved.

It is claimed that more cases of the disease are found among persons living in cities and that it is more frequent in the months from August to January. It is more frequent in men than in women and in the middle decades of life.

Special Pathology.—The essential effects produced in the tissues by actinomyces are suppuration and tissue destruction, combined, in most cases, with new formation of granulation and connective tissue. In some cases the new formation of connective tissue may be excessive in amount, and thus simulate a neoplasm. The granulation tissue usually contains many large cells filled with fat globules. Giant cells may also be present.

The area of tissue affected by a given vegetation or colony of *Actinomyces bovis* is usually many times greater than the colony, the poisonous and irritative action of the parasite affecting a wide area of the surrounding tissue. Almost any organ or part of the body may be the seat of the lesions. The extension of the actinomycotic process takes place both by continuity of the lesions and by metastases, the latter almost always occurring by way of the bloodvessels. In the lung the process may also be disseminated by way of the bronchi. The extension by continuity probably takes place by means of the separation from a colony of filaments and fragments of the microorganism, and the transportation of these in some unknown manner into the neighboring tissue, where they form new colonies and produce more foci of suppuration, tissue destruction and inflammatory reaction on the part of the surrounding connective tissue. In this way large portions of an organ or region may become replaced by granulation and connective tissue, enclosing pus cavities; or large abscesses may be formed having the characters of cold abscesses. The small abscesses enclosed in the granulation and connective tissue often communicate with one another and may form sinuses discharging pus and inflammatory products. The small abscesses, with their associated connective tissue, may become very numerous and closely set together so that a focal lesion may arise, having the gross appearance of a sponge-like mass of connective tissue saturated with pus. This is typically seen in actinomycosis of the liver. A wide extension by continuity over extensive areas and to distant portions of the body, and the formation of suppurative tracts and of sinuses, opening either on the skin or in mucous membranes, is a marked feature of the disease. Another marked feature is that the older lesions may heal by cicatrization and the dying out and

absorption of the microörganism, so that it may happen that the starting point of an extensive process may be difficult or impossible to find. Complete healing may occur spontaneously through the death and destruction of the microörganism in the lesions and by its extrusion from the body by the way of sinuses or fistulae.

Extension by metastasis takes place by the rupture of a focal lesion into a bloodvessel, thus discharging the parasite into the circulating blood, whereby the lesions may be widely disseminated throughout the body, affecting first the lungs, if a vein of the systemic system is involved, or the liver, if a vein in the portal system. Among many other possible localizations of metastatic lesions, the brain, the heart and the extremities may be mentioned. In the heart the lesions may take the form of tumor-like masses projecting into its cavities from the walls. In these embolic disseminated cases, the process may have the character of multiple subacute abscess formation and thus be essentially a subacute pyæmia. Extension by the lymphatics and involvement of lymphatic glands is very exceptional, if it occurs at all.

In extensive chronic cases amyloid infiltration may occur. Carcinoma has been observed to develop in old lesions in a few cases.

According to the point of origin or the principal location of the lesions, four forms of the diseases may be differentiated; *viz.*, head and neck, thoracic, abdominal and cutaneous.

Actinomycosis of the Head and Neck.—More than half of all the cases in man are of this form. It includes those in which are involved the structures in relation with the buccal and pharyngeal cavities, the tongue, the soft parts and the skin of the face and neck, the bones of the skull and jaws, the larynx, the thyroid, the lachrymal ducts and the brain. In these cases there may be extension to the meninges and brain through the skull or down the prevertebral space to the mediastinum and more distant parts. With the exception of the localizations in the lachrymal duct and in the brain by metastasis, it seems probable that the process in nearly all, if not all, cases of this form of the disease originates in the tissues immediately about the buccal and pharyngeal cavities. Cases in which this mode of origin is not obvious may be explained by the healing of earlier lesions. So-called primary cutaneous actinomycosis of the head or neck is open to question as to its origin in the skin in these situations. Lesions in the brain are usually metastatic. Only one case of apparently primary actinomycosis of the brain is known.

The muscular, bony and other tissues may be extensively replaced by granulation and connective tissue enclosing suppurative foci, abscess cavities, and sinuses. The inflammatory tissue and infiltration may be excessive in amount, characteristically forming brawny indurations or sarcoma-like infiltrations and swellings in the parts affected. The skin over these may be œdematous, of a bluish or reddish color, and may present projecting folds or elevations with furrows between. Here and there points of suppuration, or the orifices of sinuses surrounded by red granulation tissue, may be apparent. In less extensive cases the inflammatory process may be insignificant and may heal spontaneously. Primary involvement of the jaw bones is rare. In the brain the lesions may be like abscesses or cystic cavities filled with a gelatinous grayish-yellow substance.

Thoracic Actinomycosis.—About 15 per cent. of all cases in man are of this form. In most cases the lungs are the seat of lesions which consist chiefly of abscess and cavity formation, usually combined with the growth of granulation and connective tissue at the expense of the pulmonary tissue, so that larger or smaller portions of the lungs may be transformed into fibrous tissue permeated with cavities and sinuses. The cavities, as a rule, are small. The inferior are more frequently affected than are the superior lobes. Lesions of the bronchi may be extensive. The rupture of a focal lesion into a bronchus often leads to dissemination of the process by way of the bronchial tree. The disease may originate in the bronchi, from the œsophagus, or from lesions involving the neck by extension downward into the mediastinum, or by extension upward from lesions in the abdomen, or by metastasis. From these situations the process may extend widely and involve the lungs and thoracic wall, producing retraction and deformity of the chest.

The initial and intermediate lesions in the evolution of the process may be healed and be neither obvious nor demonstrable. Cases of so-called primary cutaneous actinomycosis of the thorax probably represent an extension from within outward. The extension of the process through the wall of the thorax and the production on the exterior of the body of swollen and indurated areas in which are the orifices of sinuses, are characteristic features of this form of actinomycosis. These sinuses may open in the epigastrium as well as on the thorax.

In the pleural cavities an accumulation of serous fluids may occur, and empyema has been observed. The disease may extend from the mediastinum to involve the pericardium and heart. As in the lung, the lesions consist essentially in extensive replacement of the natural structures of the parts by inflammatory tissue in which are abscesses and sinuses.

Abdominal Actinomycosis.—About 20 per cent. of all cases in man are of this form. Any organ or region of the abdominal portion of the body may be affected and the lesions are very varied in character. The process may arise by extension from the thorax, by metastases or by infection from the gastro-intestinal canal. It is probable that primary actinomycosis of the abdomen is always due to infection from the stomach or intestines and that the starting point in these situations, when not demonstrable, has been a lesion that has healed. Primary lesions in the intestine appear as ulcerative processes.

The most frequent localization of the primary disease in the abdominal form is in the region of the cæcum and vermiform appendix. From the intestine the disease usually extends—producing fibrous adhesions, suppurative foci and abscesses between intestinal coils—to the abdominal wall, most frequently in the right anterior half. Here the muscular and other tissues become replaced by inflammatory connective tissue in which are abscesses, sinuses, and intestinal fistulæ. The portions of the abdominal wall involved becomes brawny, and the amount of inflammatory connective tissue produced may give the appearance of a fibrous neoplasm. The skin over the affected region may be red, œdematous, and contain fluctuating suppurative foci which by their rupture become the orifices of sinuses and fistulæ.

Peritoneal abscesses may rupture into the intestine or bladder. From the abdominal wall the process may travel further and produce extensive

suppurating necrotic tracts extending through the crural ring or along the psoas muscle to the hip-joint. The process may also spread from the intestinal canal along the retroperitoneal tissues, producing extensive destruction of the muscles and bone in this region, and eventually involve the thorax, or extend down into the ischio-rectal fossa and perforate the skin in the region of the anus. Any of the abdominal or pelvic organs may become involved by direct extension of the process.

A frequent location of the lesions is in the liver, in which the foci may be single or multiple and are sometimes of large size. The lesions in the liver present the appearance of a sponge-work or honeycomb structure of connective tissue saturated with pus. They frequently arise from metastasis through the portal system as well as by direct extension. Cases of so-called primary actinomycosis of the liver have probably arisen by metastases from healed or unrecognized lesions involving the portal system of veins. Metastatic lesions in abdominal actinomycosis arising from foci outside of the abdomen most frequently occur in the spleen, kidneys, and abdominal wall.

Cutaneous Actinomycosis.—This form includes those comparatively rare cases in which the lesions are regarded as primary in the skin. As already suggested, some of these cases represent secondary invasion of the skin from deeper structures. The lesions are ulcerative or may have great resemblance to lupus and to certain forms of cutaneous syphilis. The process is essentially a local one and is outside of the scope of this article.

Symptoms.—In a disease with such a great variety of localizations and of such varying extent, it is impossible within the scope of this article to give an adequate account of all its signs and symptoms. These in general are like those of a subacute or chronic inflammatory process, or of a malignant neoplasm. In many cases the disease is far advanced and has extensively invaded important internal organs and regions before any symptoms are apparent.

In cases involving the external soft parts, prominent signs are swellings and indurations of the infected region in which suppurative foci, often recurrent, may develop, break through the skin and become the orifices of recurrent sinuses and fistulæ. The skin over the affected part may be œdematous, discolored, and warm, or the swelling may have no inflammatory character and simulate a neoplasm. Fever and pain may or may not be present.

In the frequent cases in which the disease affects the temporomaxillary region the prominent symptoms are trismus, pain, swelling, and limitation of motion of the jaws. Involvement of the skin of the neck is characterized by ridge-like elevations, or folds with sulci between, associated with the orifices of sinuses. The lesions in the tongue are usually nodular or tumor-like.

Lesions of the brain, spinal cord, or meninges may give rise to all the various signs and symptoms of meningitis, encephalitis, myelitis, cerebral thrombosis, and tumor.

In those cases originating in any region of the body with extensive suppuration or with metastases, the symptoms are usually those of pyæmia, with chills, sweats, fever, pain, vomiting, and diarrhœa. In such cases the primary process may not be obvious until the autopsy.

In the thoracic form definite symptoms and signs are usually wanting until the disease is far advanced. If the lungs are extensively involved

there is cough with foetid, sometimes bloody, sputum, and signs of bronchitis, pulmonary consolidation and cavity formation. These usually are in the inferior portions of the lungs. There is also cachexia, anæmia, fever of a variable type, and the habitus of pulmonary phthisis. The frequent involvement of the pleura and thoracic wall is a marked feature of this form of the disease and may give rise to the first symptoms. A prominent symptom of this localization is pain in the affected region. Retraction of the thoracic wall, signs of pleuritis, progressive emaciation, weakness, diarrhœa, night sweats, and fever may be present. The presence of an inflammatory swelling or a board-like induration in the wall of the thorax or epigastrium, with suppurative foci or sinuses in it, is very characteristic.

Lesions of the œsophagus have been attended with pain on swallowing or pain behind the sternum.

In primary abdominal actinomycosis the most conspicuous sign in the majority of cases is a deeply seated tumor-like mass or a hard infiltration, involving the abdominal wall, in the midst of which may be fluctuating foci or orifices or sinuses and intestinal fistulæ. The skin over the affected part may be red to brown in color and may be the seat of ulcers. Usually the affected region has a board-like consistence and is only slightly painful on pressure. The tumor-like masses are only slightly movable. The right half of the abdomen is most frequently involved, commonly in the ileo-cæcal region. The left half is less frequently involved, while localization of the lesions about the umbilicus or in the lumbar or gluteal regions is rare. These local signs may or may not be preceded or accompanied by intestinal colic, vomiting, fever, diarrhœa, constipation, swelling of the abdomen, and pain referred to the ileo-cæcal region or elsewhere.

The clinical course of the disease may be acute, with much fever and pain, as in the disseminated embolic forms, or it may be subacute or chronic with little or no pain and fever. Any of the types may develop from one of the others. Fever may occur at any time. The spleen may be enlarged.

In the chronic cases especially, there may be anæmia, diarrhœa, emaciation, weakness, œdema, and cachexia. Ascites rarely occurs. In cases in which the liver is extensively involved the organ is enlarged, but there may be little fever and but little pain referred to it. Pain in the lower ribs, jaundice, and constipation may be present. An abscess may be evident in the right hypochondrium, and there is the fever curve of supuration. Sometimes there is a painless tumor at the right costal border, with only moderate fever. Involvement of the urinary tract may produce symptoms of cystitis and pyelonephritis.

Diagnosis.—So closely does actinomycosis simulate various inflammatory conditions and tumor formations that the diagnosis is definitely established only by the demonstration of the characteristic microörganism in the lesions, or in the pus aspirated or discharged from them. The characteristic granules are rather to be sought for in the pus or discharges from the lesions than in pieces of excised tissue, because the granules or vegetations commonly exist in little cavities or sinuses in the tissue, from which they readily escape and are lost, or in which they may be concealed and elude observation owing to the small size of the granule as compared with the mass of the lesion.

The pus, or the sputum, in cases of suspected pulmonary actinomycosis, should be spread out thinly on a glass surface and the granules sought for against a dark background. A careful examination may be necessary to find them. Suspected granules should be transferred to a slide, with a small amount of water, and gently flattened under a coverglass. Under the microscope with a low power objective a typical granule appears as a brownish refringent, more or less lobulated mass or masses showing radiate striated appearances at the periphery. More or less pus adheres to the granule so that the masses of the parasite are seen to be surrounded by pus cells. Under an objective of medium magnifying power the peripheral portions of the granule are seen to be composed of the characteristic refringent radiating club-shaped bodies or filaments closely packed together and the central portions are seen to be granular or hyaline. In some instances the clubs may not be present and filaments only may be apparent at the margin.

Granules composed of conglomerates of various bacteria, such as may be observed in pus from inflammatory processes about the mouth, should not be mistaken for granules or colonies of actinomycetes. Cases of this kind have been called pseudo-actinomycosis. The same name has been erroneously applied to genuine actinomycosis, because the granules failed to show the "clubs." If the granules do not show the "clubs," the demonstration in smear preparations made from them of truly branched filaments, like those of actinomycetes, is sufficient to justify the diagnosis of actinomycosis. This is best done by breaking up one or more of the granules on a coverglass so as to form a smear preparation, staining it by Gram's method and examining it with an oil-immersion objective. In addition to longer and shorter irregularly staining filaments, often branched and occurring singly or in groups or in masses, coccus-like or bacillus-like forms may be seen. These are either products of disintegration and generation of the filaments of actinomycetes or are true micrococci and bacilli that have been growing in symbiosis with them. The coccus-like forms have been erroneously regarded by some writers as spore-like reproductive elements of actinomycetes.

The pus of closed suppurative foci is most favorable for the finding of the microorganism, and the first drops of pus or inflammatory fluid which issue from the focus are best to examine, for the granules are usually most numerous therein. They may be very few and difficult to find in the inflammatory fluid that may be expressed later from the lesions. The secretions from open sinuses may be very poor in granules and, in suspected cases with sinus formation, it may be necessary to examine the secretion accumulated during some time before the granules are found. This may be conveniently done by plugging the sinuses with a wick.

The existence of subacute or chronic indurated swellings, associated with recurrent suppurative foci or sinuses or fistulae in any situation, is suggestive of actinomycosis.

Actinomycosis of the neck and head may be confounded with any of the tumors or inflammatory conditions occurring in these parts, especially with sarcoma of the jaw. In every inflammatory process about the mouth or pharynx actinomycosis should be considered. Actinomycosis of the tongue may be confused with cancer and other conditions. Actinomycosis of the brain may be suspected only when cerebral symptoms occur in as-

sociation with a focus of known actinomycosis elsewhere. Actinomycosis of the thorax may simulate every inflammatory or neoplastic affection of that part of the body.

In cases involving the lung without obvious lesions of the thoracic wall, the disease is most likely to be confused with pulmonary tuberculosis from which it differs clinically practically only in the more frequent localizations of the signs in the inferior lobes and in the less frequent occurrence of hæmoptysis. In these cases the diagnosis can be made with certainty only by finding the characteristic granules or colonies of actinomyces in the sputum or in the pleural exudate. The sputum in all cases of chronic pulmonary disease in which tubercle bacilli cannot be found, should be examined for actinomyces. The granules usually sink to the bottom of the sputum receptacle. Any concretions in the sputum should be carefully examined.

The early symptoms of the disease may be those of typhoid fever or influenza accompanied by pleuritis, and the persistent pulmonary symptoms may be regarded as sequelæ of these affections. In cases in which the thoracic wall or vertebral column is involved the disease may simulate chiefly tuberculosis or secondary carcinoma of the spine, or sarcoma or cold abscess of the thoracic wall.

Involvement of the œsophagus may simulate cancer of that organ.

Abdominal actinomycosis may simulate a great variety of diseases and conditions, among which may be mentioned tumors, gumma, and phlegmon of the abdominal wall, appendicitis, typhoid fever, carcinoma of the intestines, tuberculosis of the ileo-cæcal lymph nodes, abscess of the liver, psoas abscess, perinephric abscess, and sarcoma of the iliac bone. If neither superficial suppurative foci, nor sinuses, nor fistulæ exist, it is possible that the actinomyces granules might be found in the fæces or in the urine, if the bladder be involved in the process.

Prognosis.—The prognosis in actinomycosis depends chiefly upon the extent and localization of the lesions. In nearly all cases the disease is chronic, lasting for months and years. Some cases recover spontaneously but for the great majority treatment is necessary to make recovery possible.

In cases affecting the head and neck the general prognosis is much better than in the other forms. Poncet and Berard¹ state that three-fourths of these cases get well. Of the 49 cases analyzed by Leiblein,² 3 died and 36 recovered. Of 52 cases treated by v. Baracz,³ 45 recovered and the fate of 7 was unknown. Heinzelmann⁴ has recently reported that of 39 cases treated surgically, 35 apparently were cured and 1, or possibly 2 had died of the disease. Of the 53 American cases analyzed by Erving⁵ 36 had recovered and 5 had died. When the disease involves the superior maxilla and the pharynx the prognosis is not as good as in the generality of the cases involving the head and neck.

¹ *Traité Clinique de l'Actinomycose humaine, Pseudo-Actinomycose et Botryomycose*, Paris, Masson et Cie, 1898.

² *Beitr. z. klin. Chir.*, XXVIII, 198.

³ *Arch. f. klin. Chir.*, 1902, LXVIII, 1050

⁴ "Ueber Endresultate bei der Behandlung der Aktinomykose," *Inaug. Diss.*, Tübingen, 1903.

⁵ *Bulletin of the Johns Hopkins Hospital*, 1902, XIII, 261.

Recurrences are not infrequent after operation or apparent cure, and a case should not be regarded as cured until two years have elapsed without recurrence. Thus Heinzelmann reports that 6 out of 31 cases had suffered recurrence before a cure was effected.

The prognosis in the thoracic form is bad. As in nearly all of the cases of the thoracic form the lung is involved, statistics bearing upon prognosis in this form deal chiefly with pulmonary actinomycosis. Of 34 cases collected by Hodenpyl,¹ all died except 2. Among 58 cases collected by Illich,² no recoveries are recorded. Of the 20 American cases collected by Erving, 15 died and but 2 recovered. Apparently only about half a dozen cases of pulmonary actinomycosis are recorded in the literature in which a recovery is claimed. In most of these the permanency of the recovery is doubtful.

In abdominal actinomycosis the prognosis is not good but it is better than in the thoracic form. It is especially bad if the retro-peritoneal tissues are involved. It is better if the process is localized in the anterior abdominal wall, is accessible to surgical treatment, and the visceral involvement is lacking or not extensive. Of 64 cases analyzed by Harz,³ 22 died and 22 recovered. Of 107 cases reported by Grill,⁴ of which 77 were treated surgically, 22 recovered and 45 died. Löwe⁵ selected 67 cases in which the disease was localized about the ileo-cæcal region and found that 12 recovered and 36 died. Of the 23 American cases analyzed by Erving, 10 died and 5 recovered. At least 1 case of spontaneous recovery is known.

Treatment.—The weight of experience in the treatment of actinomycosis is in favor of surgical means combined with the internal administration of large doses of iodide of potassium continued over long periods of time. The favorable effect of this drug in many cases seems to be generally admitted. It is said to cause more or less absorption of suppurative foci and to facilitate the discharge of the specific infectious agent from the tissues. It seems also to inhibit the development of new suppurative foci. Cures are claimed to have been effected by the use of this drug alone. It is said to act less favorably in pulmonary actinomycosis than in other forms. It must be given in the largest doses that can be borne. Favorable effects may not be apparent in the lesions until its administration has been continued for a considerable length of time. Treatment with the x-rays combined with the internal administration of large doses of potassium iodide has been highly recommended.

Opinion is divided as to the character of the surgical treatment. Some advocate the radical excision of the diseased tissue when the character of the case admits of it. Others believe that wide opening and drainage of abscesses, sinuses, and fistulæ, with or without thorough curetting, is sufficient. With the latter mode of treatment tamponades of iodide of potassium and of various antiseptics have been advocated, such as tincture of iodine, corrosive sublimate, sulphate of copper and nitrate of silver.

¹ *New York Medical Record*, 1890, XXXVIII, 653.

² *Beitr. zur Klinik der Aktinomykose*, 1892, Wien.

³ *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.*, 1900, III, 561.

⁴ *Beitr. z. klin. Chir.*, 1895, XIII, 551.

⁵ "Statistisches und Klinisches zur Kenntniss der Actinomykose des Wurmfortsatzes und des Cæcums," *Inaug. Diss.*, Greifswald, 1904.

In localizations about the jaw, any carious teeth that seem to be in relation with the lesions should be extracted. For rectal actinomycosis, Poncet has recommended the thermocautery.

Recurrence is frequent in cases treated by simple incision and drainage and it may occur even after the most radical procedure, so that repeated operation may be necessary before a cure is effected. As a prophylactic against recurrence a course of treatment with iodide of potassium has been advocated. This has also been advised as a preliminary to surgical treatment in cases with extensive lesions, as in abdominal actinomycosis, because its effects on the lesions tend to make the suppurative foci more evident, and thus more easily found and evacuated by operation. The internal administration of arsenic and of sulphate of copper has also been advised in place of iodide of potassium.

V. Baracz recommends in circumscribed lesions, especially those about the face and neck, where it is desirable to avoid cicatrices for cosmetic reasons, the parenchymatous injection of tincture of iodine, or of a 20 per cent. solution of nitrate of silver without extensive surgical interference, one cc. or sixteen minims of either of these to be injected into the lesions repeatedly every few days. One case of pulmonary actinomycosis is claimed to have recovered under treatment with oil of eucalyptus. According to v. Baracz the surgical treatment of pulmonary actinomycosis has not given hopeful results.

CHAPTER XVI.

NOCARDIOSIS, MYCETOMA, OIDIOMYCOSIS, BLASTOMYCOSIS, PULMONARY ASPERGILLOSIS, MYCOSIS MUCORINA.

By JAMES HOMER WRIGHT, A. M., M. D., HON. S. D. (HARV.)

NOCARDIOSIS.

Definition.—A considerable number of cases of inflammatory character, due to infection with branched filamentous microorganisms more or less similar to *Actinomyces bovis*, are recorded in the literature and have been the source of much confusion. A few of these cases are infections with branched tubercle bacilli or are cases of pulmonary gangrene associated with so-called branched bacilli, the pathogenic significance of which is doubtful; these need not be further considered here.

Excluding a few cases, which are more or less probably genuine actinomycosis, in which the infecting microorganism had not developed the characteristic "clubs," and some cases that are very meagerly reported, there remains a considerable group of cases which either have been shown, or may at present be assumed, to be cases of infection with different species of a single genus of microorganisms the chief characters of which are described below. To the cases in this group the terms pseudotuberculosis, or streptothrix, or cladothrix infection, or atypical actinomycosis have been applied. None of these names are satisfactory. Pseudotuberculosis is too indefinite a term and carries no etiological suggestion with it. Streptothrix and cladothrix are generic terms that are untenable for the group of infecting microorganisms in question, for they are well recognized generic names for microorganisms quite different from these. Atypical actinomycosis is objectionable, because it leads to the confusion of these cases with actinomycosis and because it implies that the infection microorganism is so closely related to *Actinomyces bovis* as to be classed in the same genus with it.

This idea of the close relationship of the infecting microorganism in these cases to *Actinomyces bovis* is widely accepted, but the writer¹ has shown that it is erroneous and that *Actinomyces bovis* differs so markedly from the microorganisms of this group that it should not be placed in the same genus with them.

It has been pointed out that if the name *Actinomyces* be not used for these microorganisms then the only permissible generic term to apply to them, in accordance with the principles of botanical nomenclature, is *Nocardia*,² and disease processes produced by them should be called

¹ *Journal of Medical Research*, 1905, XIII, 349.

² *De Toni et Trevisan. Saccardo. Sylloge Fungorum*, VIII, 927.

nocardiosis. In accordance with this view these cases are grouped together under the name nocardiosis and the infecting microorganisms will be called *Nocardia* in this article.

The first description, although an imperfect one, of a nocardia is that of Cohn,¹ who found it in a concretion in the lachrymal duct and gave it the untenable generic name of *Streptothrix*. The first extensive study of a case of nocardiosis was that of Eppinger,² in 1891.

Etiology.—The nocardia, the infecting microorganisms in nocardiosis, have resemblances, on the one hand, to certain bacteria in the structure, thickness, and staining of their filaments, and, on the other hand, to the hyphomycetes or moulds in their branching, thread-like form and in the production of fine conidia or spore-like reproductive elements out of the substance of the filaments. They differ from the hyphomycetes in that their filaments are more slender and are not tubular structures with double contoured walls, protoplasmic contents, and transverse septa. They may be regarded as representing a further transition from the bacteria toward the lower fungi or hyphomycetes than does *Actinomyces bovis*, because they have this property of producing spore-like reproductive elements or conidia, a property not possessed by that microorganism.

Most of the known species grow readily on the ordinary culture media, are aerobic and do not require the temperature of the body for their multiplication. They grow in dense masses on culture media, on which the younger colonies may appear as aggregations of filaments radiately arranged. They are widely distributed in the outer world, especially in the air and on grains and grasses as shown by the work of Doria,³ Berestneff,⁴ and others. The various species differ chiefly in the color and other appearances of their growths on artificial culture media.

It is very probable that the nocardia, claimed to have been isolated from certain cases of inflammatory lesions as well as from certain cases of typical actinomycosis, gained entrance to the culture tubes by accident or were secondary invaders of the lesions. Among such nocardia are those microorganisms described by Rosenbach,⁵ Naunyn,⁶ Almquist,⁷ Bostroem,⁸ Vincent,⁹ and others. *Nocardia* have been observed in the sputum of apparently healthy individuals.

Infection seems to take place most frequently through the respiratory tract. In three cases it has occurred from wounds. Malnutrition and chronic disease seem to predispose the individual to this infection as to others. Including four animal cases, there are some twenty well authenticated cases¹⁰ of infection with nocardia from which the microorganism

¹ *Beitr. z. Biolog. d. Pflanzen*, 1875, I, 141.

² *Beitr. z. path. Anat.*, 1891, IX, 276.

³ *Ann. dell' Inst. d'Igiene speriment., della R. Univ. di Roma*, 1892, II, 167.

⁴ *Zeitschr. f. Hyg. u. Infektionskrankh.*, XXIV, 94.

⁵ *Archiv. f. Klin. Chir.*, 1887, XXXVI, 346.

⁶ *Mitth. a. d. Med. Klinik*, I Königsberg, Leipzig, 1888, 296.

⁷ *Zeitschr. f. Hyg. u. Infektionskrankh.*, 1890, VIII.

⁸ *Beitr. z. Path. Anat. u. z. allgem. Path.*, 1890, IX.

⁹ *Ann. de l'Inst., Pasteur*, 1894, VIII.

¹⁰ Eppinger, *Ref. Zeigler Beitr. z. path. Anat.*, 1890, IX. Dessy, *La Settimana medica dello "Sperimentale"*, Firenze, March 28, 1896, 156. Aoyama and Miyamoto, *Mitth. a. d. med. Facultät d. kaiserl., japanisch Univ. z. Tokio*, 1902, IV, 231. MacCallum, *Centralbl. f. Bakteriöl.*, I Abt., 1902, XXXI, 529. Birt and Leishman, *Jour. Hyg.*, 1902. Trolldener, *Zeitschr. f. Thiermed.*, 1903, XVII,

has been isolated and studied in pure culture. In a smaller number of cases¹ regarded as nocardiosis, culture experiments have not been successful or were not attempted.

The nocardia isolated in the cultures have shown sufficient differences among themselves to be regarded as belonging to various species.

Analysis of the better studied cases shows that the microorganisms from at least eleven of the human cases and from one case in a dog were sufficiently alike to be considered as probably belonging to the species first described by Eppinger, who gave it the specific name of "asteroides" and the untenable generic name of *Cladothrix*. This species is characterized by the reddish color of its growths on culture media, by not liquefying the gelatin and by producing so-called pseudotuberculosis in animals inoculated with it. The lesions in these animals consist of foci of suppuration surrounded in typical instances by more or less well developed granulation tissue. They may be very extensive and widely disseminated throughout the body. A marked peculiarity of most of the microorganisms concerned in nocardiosis is their resistance to decolorization by weak acids after being stained by fuchsin.

The wide distribution of the nocardia in the outer world has already been referred to and it seems very probable, in view of the biological characters of those that have been isolated from pathogenic processes, that they likewise have a natural habitat outside of the body.

Special Pathology.—The lesions ascribed to the action of nocardia are of varied character. There is no doubt that these microorganisms produce necrosis, suppuration, abscesses and granulation tissue formation as well as miliary focal lesions that are essentially suppurative foci surrounded by more or less granulation tissue, but it is not proven that fibrous or calcareous nodules, areas of caseation and tubercles identical in structure with those of tuberculosis, can be produced by them. The best evidence in favor of the idea that lesions, histologically identical with those of tuberculosis, may be produced by them is offered by Flexner; but the microorganism in his case was not studied in cultures, and it is therefore not certain that it was a nocardia. The filaments of the infecting microorganism in nocardiosis are scattered among the cells of the lesions or are loosely grouped together, and are not aggregated so as to

81. Horst, *Zeitschr. f. Heilkunde, Abth. f. path. Anat.*, 1903, XXIV, 157. Tuttle, *Med. & Surg., Rep. Presbyterian Hospital*, N. Y., 1904, VI, 147. McDonald, *Scot. Med. & Surg. Jour.*, 1904, XIV, 305-321. Schabad, *Zeitschr. f. Hyg.*, 1904, XLVII, 41. Stokes, *Am. Jour. Med. Sci.*, 1904, CXXVIII, No. 5, 861. Menmo, Quoted by Rullman, *Munch. med. Wochenschr.*, 1898, No. 29, 920. Berestneff, "Die Aktinomykose und ihre Erreger," (Russian), *Inaug. Diss., Moskau*, 1897. Scheele and Petruschky, *Deutsch. med. Wochenschr. Vereins beilage*, 1897, No. 17, 124. Sabrazès et Riviere, *La Sem. Med.*, 1895, 383. Ferre and Farquet, *La Sem. Med.*, 1895, 359. Nocard, *Ann. de l'Inst. Pasteur*, 1888, II. Kruse and Pasquale, *Zeitschr. f. Hyg.*, XVI. Terni, *Ref. Centralbl. f. Bakteriolog.*, 1896, XIX, 160. Ophüls, *Jour. Med. Research*, 1904, VI, 439. Mayer, *Munch. med. Wochenschr.*, 1901, No. 44. Saint Servin, *La Sem. Med.*, 1895.

¹ Flexner, *Jour. Exper. Med.*, 1898, III. Warthin and Olney, *Am. Jour. Med. Sci.*, 1903, Oct., 637. Buchholz, *Zeitschr. f. Hyg.*, 1897, XXIV. Ohlmacher, *Cleveland Med. Jour.*, 1902, 29. Rullman, *Munch. med. Wochenschr.*, 1898, No. 29, 920. Uecke, *St. Petersburg med. Wochenschr.*, 1901, XVIII, 87. Rabe, *Berlin Thier. Wochenschr.*, 1888, 65. Butterfield, *Jour. Infect. Diseases*, 1905, II, 421. Musser and Gwyn, *Trans. Assoc. American Physicians*, 1901, XVI, 208.

form the compact masses or radiate structures or granules that are characteristic of actinomycosis.

The process in most of the cases has been situated in the lung or has originated there. In the lungs pneumonia, abscesses, gangrene, indurative processes, fibrous nodules, cavities, caseous pneumonia, miliary tubercles, and other lesions like those of tuberculosis, have been described. As has been already pointed out, it is uncertain whether these lesions, like those of tuberculosis, are due to nocardia rather than to the tubercle bacillus. In two cases the reporters considered tuberculosis to be coincident.

Metastatic lesions have been observed in nine cases, among which the brain, myocardium, lung, kidney, peritoneum, lymphatic glands and subcutaneous tissue have been involved. The primary process was in the lung in five of these cases; in a bronchial gland in one or two; in the region of the knee-joint in one; and was unknown in one. In six cases there were one or more abscesses in the brain. In two cases there was empyema and pericarditis. One case was of the nature of a subacute purulent peritonitis. Conjunctivitis and subcutaneous abscess have also been ascribed to infection with nocardia. In the animal cases there was suppuration in various regions.

Symptoms.—The symptoms, as far as has been ascertained from the reports, have been in general those of suppuration or inflammation and have varied with the location and extent of the process. The clinical course was either acute or chronic.

In most of the pulmonary cases the signs and symptoms have been those of pulmonary tuberculosis or of pneumonia and abscess. Cough, fever, pain, and emaciation have been observed. In two cases there was hæmoptysis. Signs of empyema were present in two cases, in one of which there was an inflammatory fluctuating tumor on the external aspect of the chest wall. In one of these cases also, signs of pericarditis were made out. In two cases there were multiple metastatic abscesses in the subcutaneous tissue with symptoms of pyæmia. In one of these infection with the bacillus of glanders was suspected.

In a few cases the process has been essentially of the character of a terminal infection. In three of the cases in which there was abscess formation in the brain, there were symptoms of tumor and abscess in two, while in one the diagnosis of tuberculous meningitis was made. In the case of subacute peritonitis which followed gastrotomy, the prominent symptom was diarrhœa.

Diagnosis.—Nocardiosis may be confused with a variety of diseases, but especially with pulmonary tuberculosis and actinomycosis. In cases with multiple abscess formation in the subcutaneous tissue, the disease may simulate infection with the bacillus of glanders. The diagnosis depends upon finding the special microorganism in the sputum or in the lesions. It occurs typically in the form of branched filaments of the character above described, which resist decolorization by dilute acids after having been stained with fuchsin. Fragments of the nocardia may be mistaken for tubercle bacilli, especially for the rare branched forms of that microorganism.

The nocardia may be distinguished from the tubercle bacillus by their longer filaments and more marked branching and also by their occurrence

in loose aggregations. A further distinction lies in the fact that most of the nocardia after staining with fuchsin do not resist decolorization with acids as strongly as does the tubercle bacillus, and are decolorized by alcohol, whereas the tubercle bacillus is not. Probably the best way of finding nocardia in sputum or pus is by the microscopic examination of smear preparations stained by Gabbet's method, for this does not employ alcohol and is not a very vigorous discolorizer.

The nocardia are distinguished from the microorganism of actinomycosis in that they do not occur in the inflammatory fluids or lesions in man in the compact masses nor form the radiate club-bearing structures or granules so characteristic of actinomycosis. Moreover, the microorganism of actinomycosis does not resist decolorization by dilute acids after having been stained with fuchsin. Localization of the lesions about the mouth and jaws, so common in actinomycosis, is unknown in nocardiosis.

Prognosis.—All of the cases in which the lung or brain was involved died except two, which got very much better or recovered. These two cases were among the less well authenticated ones.

Treatment.—No specific is known and the treatment will vary with the character of the process and the situation of the lesions. In cases resembling pulmonary tuberculosis the treatment should be essentially the same as for that disease. Empyema and abscesses should be treated according to the usual surgical principles.

MYCETOMA (MADURA FOOT).

Definition.—Mycetoma is a chronic infectious process, most commonly affecting the foot, the prominent features of which are multiple sinuses and enlargement and distortion of the parts. Carter¹ first assigned to the disease a separate identity and a special parasitic causation. He gave it the name Mycetoma.

Etiology.—The affection is characterized by the presence, in the diseased tissue and in the discharges from sinuses, of peculiar granules usually not more than 1 mm. in diameter but sometimes larger. In certain cases these granules are of a black color, of irregular shape, hard, rather brittle, and, in general, resemble grains of gunpowder. In other cases the granules are whitish, grayish or yellowish in color, of a soft or cheesy consistence, and have been compared to fish roe in appearance. A few cases are also recorded in which the granules were of a red color.

According to the observations of Carter and others, the granules are composed of aggregations of vegetable parasites and their products. On account of their relation to the lesions the granules are presumed to be the infectious cause of the disease and not merely secondary invaders of the lesions. They have not been shown by experimental inoculation to be capable of producing the disease. On account of the fact that at least two very different kinds of granules are found associated with the lesions, two varieties or forms of the disease are recognized: the "melanoid" or black variety, in which the granules are black, and the "ochroid" or pale variety, in which the granules are white to yellow in color.

¹A. V. Carter: *On Mycetoma or the Fungus Disease of India*, London, 1874.

The ochroid granules, as shown by the studies of Kanthack¹ and Bishop,² are apparently identical with the granules of actinomycetes; and at the present time the ochroid or pale form of mycetoma must be regarded as actinomycosis of the part. Boyce³ and Vincent⁴ claim to have obtained cultures of the specific microörganism from two cases of this form of the disease, but their microörganisms are widely different from each other and neither of them was proved to be identical with the microörganisms in the lesions and not a secondary invader or a contamination of the cultures.

The black or melanoid granules, on the other hand, as shown by the studies of Bristowe,⁵ Carter, Wright,⁶ and others, are of entirely different character. They consist of a mass of hyaline refringent, brown-colored, brittle substance, forming a matrix in which are imbedded a tangle of fungus tubules or hyphæ with doubly contoured walls and transverse septa. This fungus of the melanoid form of the disease has been isolated in cultures by the writer from a single case. This is very probably the only instance in which its cultivation has been accomplished, for Carter's claims that he had grown the fungus in cultures do not bear critical examination. The writer obtained a growth of the fungus from about twenty-five out of approximately sixty-five of the black granules experimented with in this case.

The mode of entrance of the parasite into the tissues is not known. The disease is endemic in certain districts in India, especially in Madura, and has been observed in Africa, Italy, and other tropical or subtropical countries. It seems to be acquired in the country districts and not in towns. In America it is of very rare occurrence, only four undoubted cases having been reported, and three of these were of the pale variety of the disease, which, as has been pointed out above, is to be regarded as actinomycosis.

Special Pathology.—The process consists essentially in abscess and sinus formation, associated with extensive development of granulation and connective tissue. The granules are found in the abscesses or sinuses and sometimes they may be found surrounded by epithelioid cells and giant cells. Giant cells may be frequent in the granulation tissue. The inflammatory tissue may very extensively replace the muscles and bones of the affected part, the tendons and fascia most resisting replacement. In advanced cases the granules may exist in sinus cavities in masses. The foot is most commonly affected, but occasionally the hand and, rarely, other parts. The internal organs are never involved.

Symptoms.—The process usually begins as a firm nodular swelling in the sole of the foot, which is followed by others in the neighborhood or elsewhere. These break down and become the seat of the openings of sinuses which rarely heal. By extension of the process the foot increases in breadth and thickness and may attain a considerable bulk and weight, eventually becoming very burdensome to the patient. The toes become

¹ *Journal of Pathology and Bacteriology*, 1893, I, 140.

² Hyde, Senn and Bishop: *Journal of Cutaneous and Genito-urinary Diseases*, XIV, 1, 1896,

³ *Hyg. Rundschau*, 1894, IV, 529.

⁴ *Ann. de l'Inst. Pasteur*, 1894, VIII, 129.

⁵ *Transactions of the Pathological Society*, London, 1871.

⁶ *Journal of Experimental Medicine*, 1898, III, 421.

more or less displaced and deformed. The orifices of sinuses may be obscured by masses of granulation tissue. The discharges from the sinuses are oily, mucopurulent and may have a very bad odor. They contain the characteristic granules above described. Severe pain is rare. In advanced cases the great weight of the foot prevents its use in walking, and atrophy of the leg muscles occurs.

Diagnosis.—The disease may be mistaken for syphilis or for sarcoma. The diagnosis depends upon finding the granules and upon recognizing their characteristic structure. To cases of the pale or ochroid variety, what has been written upon the subject of the diagnosis of actinomycosis applies. The fungus elements in the black granules are best demonstrated by softening and bleaching the granules with liquor sodæ chlorati and examining teased preparations of them under the microscope. In such preparations the fungus elements should be clearly visible as septate, tubular, cylindrical or spherical structures with doubly contoured walls.

Prognosis.—The process is very chronic and may last for years. Spontaneous recovery never occurs. Death may follow from secondary infection with pyogenic microorganisms or may be due to exhaustion incident to the burden of carrying about the greatly enlarged and heavy, diseased foot.

Treatment.—The internal administration of iodide of potassium is said to have no favorable effect upon the process. The only effective treatment is excision of the lesions or amputation.

OIDIOMYCOSIS.

Definition.—A granulomatous and suppurative process affecting the skin and internal organs. It is called dermatitis coccidioides, protozoic dermatitis, blastomycetic dermatitis, psorospermiasis, coccidioidal granuloma, blastomycosis, and saccharomycosis. Apparently about forty-five cases have been reported. It is probable that some cases of this disease now go unrecognized and are classed under tuberculosis. The first cases were described by Wernicke,¹ Busse,² and Gilchrist and Stokes.³ A good description of the cutaneous forms of the disease is given by F. H. Montgomery.⁴

Etiology.—The disease is due to infection with certain fungi which although showing various differences in biological characters among themselves may, according to Ricketts,⁵ be classed as species of the genus *Oidium*. In the lesions the microorganisms appear chiefly as spherical bodies, each consisting of a protoplasmic mass enclosed in a doubly contoured hyaline capsule, which may be provided with prickles or spines in some instances. The diameter of the bodies varies up to thirty microns or more. In the protoplasm, vacuoles, granules and various markings may be seen, but no nucleus is apparent. The mode of proliferation in the lesions in the majority of cases is by gemmation or budding. The

¹ *Centralbl. f. Bakteriolog.*, 1892, XII, 859.

² *Centralbl. f. Bakteriolog.*, 1894, XVI, 175.

³ *Bulletin of the Johns Hopkins Hospital*, 1896, VII, 129.

⁴ *Journal of the American Medical Association*, June 7, 1902.

⁵ *Journal of Medical Research*, 1901, VI.

microorganisms in some cases have great resemblance to yeast fungi or saccharomyces. Busse regarded the microorganism in his case as a yeast and called the process sacchromycosis. In a minority of the known cases, proliferation of the microorganisms in the lesions is not by budding but by a process which is regarded as one of sporulation, the protoplasm of the larger forms segmenting into many small spherical bodies. Each of these small spherical bodies acquires a capsule and, being set free by the rupture of the capsule of the mother cell, develops into the adult parasite.

Wernicke, and Rixford and Gilchrist,¹ first described cases with these sporulating forms in the lesions and they regarded the microorganisms as protozoa; but, later, Ophüls and Moffitt² showed that they are stages in the life-cycle of a mould fungus. The microorganisms may be few or very numerous in the lesions. In cultures the microorganisms show considerable variation in biological character.

According to Ricketts, the microorganisms obtained from various cases may be divided into three groups according to their biological characters as shown in the cultures as follows:

1. Those growing chiefly as spherical or oval budding cells and resembling yeasts, but capable of producing mycelium.
2. Those forming submerged mycelium, which breaks up into chains of spores, while proliferation by budding is not a prominent feature.
3. Those producing mycelium with fruit-bearing aerial hyphæ and also capable of multiplying by gemmation or budding.

The microorganisms of the first and second groups are capable of producing fermentation, while those of the third group are not. In animals inoculated with cultures of some, but not all, of these microorganisms, abscesses, granulomatous tumors and tubercle-like nodules widely disseminated have been produced. In these lesions in the animals the microorganisms exist in the same form as in the human lesions.

Wolbach,³ working with a microorganism of the type which proliferates in the tissues by sporulation, has studied carefully, in animals inoculated with pure cultures, the transformation of the hyphæ of the cultures into the characteristic spherical bodies of the lesions. He finds that the spherical bodies arise by the segments of the hyphæ enlarging and assuming a spherical shape, the wall of the segment thus becoming the capsule of the spherical body. In his experimental lesions, Wolbach has also observed pointed and club-shaped hyaline bodies radiately arranged continuous with the capsules of the microorganisms.

The conditions underlying infection in oidiomycosis are not yet known. There is no definite relation between the disease and the sex, age, occupation, nativity, or habits of the patients. Most of the cases with so-called sporulating forms in the lesions have occurred in California. All of the cases except two have been observed in the United States. A few cases followed traumatism.

Special Pathology.—The process usually consists in abscess formation, combined with proliferation of the fixed cells of the infected region; but it may be characterized by the formation of caseating aggregations of

¹ *Johns Hopkins Hospital Reports*, 1896, I, 209.

² *Philadelphia Medical Journal*, June 30, 1900.

³ *Journal of Medical Research*, 1904., XIII, 53.

epithelioid cells accompanied by giant cells, thus simulating the lesions of tuberculosis. The reaction on the part of the tissue in some cases may be comparatively slight and the lesions may consist chiefly of masses of the microorganisms. Multinucleated giant cells containing the parasites are prominent features of the lesions. In the skin there is, in most cases, extensive hyperplasia of the rete mucosum, abscesses both in the corium and in the rete, and tubercle-like aggregations of epithelial cells with giant cells. The microscopical appearances may simulate squamous-cell carcinoma or verrucous tuberculosis and the microorganism may be present in comparatively small numbers. The lesions may be limited to the skin or may involve also the lungs and internal organs. The disease may take origin in the lungs. The face is most frequently the seat of cutaneous lesions, but the skin of almost any region of the body may be involved.

The skin involvement may be very extensive. There is but little tendency to involve mucous membranes. In the skin the process begins usually as a papule or pustule and slowly enlarges during the course of months, producing an elevated area, which may be of large size, with rough, scabby surface and enclosing numbers of minute abscesses. Later, ulceration occurs, and ultimately there may be cicatrization and healing. In many cases the cutaneous lesions are multiple and they may be situated in widely separated parts of the body. Involvement of the lungs, and of other organs and structures not cutaneous, has been observed in sixteen or more cases,¹ in six of which cutaneous lesions were absent. Among these cases in addition to the lungs and skin, the pleura, liver, kidneys, spleen, bones, suprarenals, testicles, peritoneum, meninges, and various lymphatic glands have been the seat of lesions. In the lungs the lesions have consisted of abscesses, miliary nodules, bronchopneumonia, and areas of consolidation. The meninges were affected in two cases and the lesions were very similar to those of tuberculous meningitis, both grossly and microscopically. In the liver, spleen, kidneys, adrenals, testicles and lymphatic glands, the lesions have consisted of small nodules, abscesses, cheesy or necrotic areas or grayish-white infiltrations. When the process has involved the bones it has been suppurative and necrotic in character, sometimes simulating tuberculosis. Amyloid infiltration has been observed in two cases.

Symptoms.—In most of the cases the disease is very chronic, lasting for years. The cutaneous lesions in most cases have periods of rapid progression interrupted by periods of relative quiescence. There may be severe pain. In cases involving the lungs and other internal organs, the symptoms and signs are very similar to those of pulmonary tuberculosis. Prominent symptoms are cough, pain, profuse expectoration, and fever, highest at night. Sweating has been observed in these cases. Eventually there is emaciation and asthenia.

Diagnosis.—The cutaneous lesions are most likely to be confounded with verrucose tuberculosis but they may also resemble carcinoma, mycosis fungoides, as well as certain forms of syphilis of the skin. The diagnosis can only be made with certainty by finding the microorganism

¹Otis and Evans, *Journal American Medical Association*, October 31, 1903, 1075; Cleary, *Transactions of the Chicago Pathological Society*, 1904, VI, 105. Ophiols *Journal American Medical Association*, October 28, 1905, p. 1291. References to other cases may be found in the papers already quoted.

in the lesions. This is best done by examining the contents of the small abscesses or a fragment of the tissue with the microscope and finding the fungus cells. A drop of the pus mixed with water or a 30 per cent. sodium hydrate solution may be placed under a coverglass and examined directly with the microscope without staining. The cases in which the lungs are involved may be regarded as pulmonary tuberculosis. The diagnosis in such cases will depend upon the recognition of the nature of any co-existent cutaneous lesions, or it might be made by finding the fungus in the sputum. Diagnosis by means of the examination of the sputum has never been made.

Prognosis.—When the disease is primary in the skin it is generally very chronic and may persist for ten years or longer. Death from involvement of the lungs and other internal organs, in cases in which the skin has been primarily the seat of the lesions, has been observed in 4 cases. As far as is known the cases in which the lungs have been involved have terminated fatally.

As regards prognosis there is a great difference between those cases in which the microorganism exists in the lesions in budding forms and those in which sporulating forms occur. Thus, of the 13 or 14 cases due to infection with the sporulating form, all came to autopsy except 4; while of the 30 odd cases due to infection with the budding forms, apparently but 4 died of oïdiomycosis.

When confined to the skin the disease yields to proper treatment, with a varying amount of cicatricial deformity. Spontaneous healing may occur, at least in some of the lesions. After the lungs and other viscera have become extensively involved the disease may terminate fatally within a few months.

Treatment.—The internal administration of iodide of potassium has been employed with considerable success in the treatment of oïdiomycosis. It should be given in large doses; 50 to 150 grains (3.75 to 10 gm.) have been given three times daily. This may be combined with treatment by the x-ray, especially in the superficial cases. Simple local antiseptic treatment of the cutaneous lesions has not given good results. It is, however, of value in relieving soreness and preventing secondary infections, as well as in cleansing the lesions. Total excision when the lesions are limited gives the best results. Thorough curetting followed by cauterization has been advised. There is some evidence, however, that curetting may lead to the general dissemination of the process. Walker and Montgomery¹ recommend the actual cautery or free excision, with deep dissection and repairs by skin-grafts or plastic operations, in those cases in which the iodide of potassium fails to cure. They do not recommend curetting. Sulphate of copper administered internally in doses of from one-fourth to one grain three times daily and applied externally as a wash in 1 per cent solution has been employed by Bevan.²

Addendum.—Closely allied to the microorganisms of oïdiomycosis is the microorganism of parasitic stomatitis, or thrush,—the *Oidium albicans*. In a very few cases this oidium has invaded internal organs and has been found in abscesses in the brain, spleen, kidney, and lung.

¹ *Journal of the American Medical Association* April 5, 1902, 867.

² *Journal American Medical Association*, November 11, 1905, 1492.

BLASTOMYCOSIS.

The yeast-like budding fungi, associated with some of the cases classed above under oïdiomycosis, are called by some writers blastomycetes; and, therefore, such cases may be called blastomycosis.

In addition to these cases, however, a considerable number of observations of the occurrence of yeast-like fungi in a variety of pathological conditions both in man and animals are on record. Of these, there are only two isolated cases in man that seem worthy of mention. They are of a very different character from the cases grouped under oïdiomycosis and, therefore, may be considered under blastomycosis. One of these cases¹ presented myxomatous tumors beneath the skin in several places. Histologically, the tumors resembled myxo-sarcoma and contained the fungi in large numbers. In the other case² sarcoma-like tumors involved the omentum and mesentery, and there was chylous ascites. In the ascitic fluid a yeast or blastomycetes was found but in the tumors it was not satisfactorily demonstrated.

In animals, several infectious processes are ascribed to blastomycetes. The most important of these is a suppurative disease in horses, resembling farcy, characterized by chronic inflammation of lymphatics and lymphatic glands in which there is proliferation and nodular thickening followed by purulent softening. The upper air passages are also involved in the process.

PULMONARY ASPERGILLOSIS.

Definition.—A destructive inflammatory process affecting the lungs, due to infection with one or more species of fungus of the genus *Aspergillus*. The first observation of the occurrence of a fungus that was probably an aspergillus, in a human lung, was made by Bennett, in 1842; but the first scientific description of cases with an exact determination of the identity of the fungus was by Virchow, in 1856.

Etiology.—The disease is due to infection with the spores of the microorganism, and the species *fumigatus* is probably the only one concerned. The spores gain entrance to the lung through the respiratory tract. The *Aspergillus fumigatus* is a true fungus belonging to the family *Perisporaceae*. In cultures it grows in the form of a mould consisting of a thick felt-work of septate tubular hyphæ, a few micra in diameter, some of which grow upward into the air and produce masses of spores at their free extremities. The spores are spherical, 2.5 or 3.5 micra in diameter and are easily transported through the air. The various species of aspergillus are common in the outer world and the spores are widely distributed on vegetable material of all kinds.

The *Aspergillus fumigatus* has been found as a harmless parasite in the auditory canal, tympanum, nose, mouth, maxillary sinuses, throat, respiratory passages, eyes, and genitalia. Sometimes it is found in an inflammatory condition of the external auditory canal, but the inflammatory process in these cases is probably due, in part at least, to the action

¹ Curtis, *Ann. d. l'Inst. Pasteur*, 1896, X, 449.

² Corselli and Frisco, *Centralbl. f. Bakteriöl.*, 1895, XVIII, 368.

of pyogenic bacteria. It is said to be capable of causing keratosis, dermatitis, a peculiar affection of the nails, rhinitis, and pharyngitis.

In various birds, and in cattle, horses, and dogs, it may be the cause of an inflammatory process more or less resembling tuberculosis in which the lesions are situated chiefly in the lungs. In birds, the liver, the kidneys, and the air sacs may also be infected and it may produce a pseudodiphtheritic condition of the mouth and air passages. The intravenous inoculation of birds and various animals with spores may produce death within a few days. The lesions produced resemble grossly those of tuberculosis. Histologically, they consist of foci of necrosis, enclosing the microorganisms, together with more or less infiltration with inflammatory cells. Infection may be produced experimentally by way of the respiratory tract in birds, and rabbits may be infected by feeding.

Most of the cases of pulmonary aspergillosis in man may be regarded as instances of secondary infection in lungs already diseased by tuberculosis or other processes, and some have been mere terminal infections. But little clinical importance was attached to pulmonary aspergillosis until the observations of Dieulafoy, Chantemesse, and Widal,¹ published in 1890, and of Renon,² published in 1897, gave good grounds for believing that it could exist as a primary disease. These writers claimed that primary pulmonary aspergillosis was frequent among the so-called pigeon feeders and hair sorters of Paris. The pigeon feeders are accustomed to feed the pigeons from their own mouths with a mixture of millet and vetch seeds in water. They are supposed to acquire the disease either from these seeds or from aspergillosis in the birds. The hair sorters work in an atmosphere charged with the dust of rye flour, which they use in considerable quantities to free the hair from grease. Birds kept in this atmosphere died in two or three days, from aspergillosis. The spores of the aspergillus are in the rye flour used and they gain entrance to the lungs directly from the air.

Important contributions to the subject have been made by Saxer.³ Good general articles upon the disease have been written by Rolleston⁴ and Sticker.⁵

Special Pathology.—The essential effects produced upon the lung tissue by the *Aspergillus fumigatus* are necrosis and exudation of leukocytes. The typical appearances are areas of pneumonic consolidation, or necrosis with a colony of the fungus in the centre. Where the colony is in close relation with a bronchus and has had a good supply of oxygen, spores are produced which may be disseminated through the lung by way of the bronchi and give rise to further extension of the process. Eventually the necrotic tissue may be sequestered and expectorated, thus giving rise to cavities with gangrenous walls. Usually bacteria do not take part in the necrotic process, and purulent liquefaction of the necrotic tissue does not occur. In typical cases there is little fœtor associated with the process. It would seem that the fungus inhibits the invasion of the putrefactive bacteria into the lesions.

¹ *Tenth International Medical Congress*, Berlin, 1890.

² *Étude sur l'Aspergilliose chez les Animaux et chez l'Homme*, Paris, 1897.

³ *Pneumonomykosis Aspergillina*, Jena, Germany, 1900.

⁴ *Allbutt's System of Medicine*, VI, 257.

⁵ Nothnagel: *Specielle Pathologie und Therapie*, XIV, 2; I. Abth. 156.

The microorganism may exist in the lesions in colonies, with a form suggestive of actinomyces; or the hyphæ may penetrate the diseased tissue more or less diffusely. The process in the lungs may become arrested and the fungus may disappear. In this case, extensive fibroid changes may result, or the lungs may become the seat of tuberculosis. Metastatic lesions are not known to occur in aspergillosis.

Symptoms.—The clinical course of the disease in the primary cases is either that of chronic pulmonary tuberculosis or of chronic bronchiolitis, emphysema, and chronic interstitial pneumonitis. In secondary cases symptoms referable to the infection with aspergillus may be absent or of little importance.

Diagnosis.—The diagnosis can only be made by finding fragments of the aspergillus or its spores in the sputum. Cultures may be necessary to establish the identity of the microorganism. The fragments of the microorganism may be found imbedded in blood clots or in masses of necrotic tissue. The sputum may resemble that of pulmonary gangrene but the characteristic factor of that process is absent. Tubercle bacilli may be found coincidently in the sputum.

It is important that the sputum be fresh, for it may be secondarily invaded by spores of the aspergillus from the air. Microscopical examination of the sputum for the fungus is facilitated by mixing a small amount of it with a 20 per cent. solution of sodium hydrate in order to dissolve the cells and tissue fragments and render the fungus elements more clearly visible.

Prognosis.—When aspergillosis is engrafted upon a chronic disease of the lungs, it usually does not seem to contribute much to the death of the individual. In primary cases the prognosis is not so bad as in pulmonary tuberculosis, but it is to be borne in mind that even if the aspergillosis is arrested and disappears, the permanent injury to the lungs may lead to eventual death or may be followed by pulmonary tuberculosis. Cases with a clinical course resembling emphysema and chronic bronchiolitis seem to have a worse prognosis than those resembling pulmonary tuberculosis.

Treatment.—In the primary cases it is of the utmost importance that the patient avoid breathing in a dust laden atmosphere, or contact with dry grains and vegetable material. The main reliance should be placed upon fresh air, good food, and tonics. The internal administration of iodide of potassium or of arsenic has been advised. In the secondary form the treatment should be that of the underlying disease.

MYCOSIS MUCORINA.

There is only one case on record of general infection with fungi of the genus mucor. This was the case reported by Paltauf in which there was found at autopsy ulcerative enteritis, pneumonia, phlegmon of the pharynx, and multiple abscesses in the brain. In the lesions a mucor was found.

The mucors are moulds, a typical example of which is the common bread mould. Their spores, when injected into the circulation of certain animals, produce effects similar to those produced by the spores of aspergillus.

PART VI.

DISEASES CAUSED BY PROTOZOA.

CHAPTER XVII.

THE PROTOZOA.

By GARY N. CALKINS, PH. D.

THE progress made during the last few years in the study of pathogenic protozoa justifies us in expecting that discoveries and advances will ultimately place the subject of protozoan pathology upon a sound scientific basis. So few malignant forms have as yet been worked out, however, that we are still constrained to seek analogies in rather distantly related non-parasitic types. Fortunately we have here a wide realm of facts which have been accumulated during more than two hundred years of study upon these unicellular forms; facts which have been collected and grouped into biological laws which we believe are applicable to all forms, parasitic and pathogenic, as well as harmless types.

The protozoa are unicellular animal organisms, which reproduce by division or spore-formation. They invariably have nuclear material, usually in the form of a definite nucleus, but occasionally scattered throughout the cell. They may live alone or associated with sister-cells in colonies of varied form, size, and complexity. They have two well-defined phases, one of vegetative activity, the other of quiescence; during the latter the organisms are protected by resistant secretions, termed cysts.

Protozoa are organisms of a different type from the bacteria with which they are often compared. The difference is not entirely covered by the usual statement that bacteria are plants while protozoa are animals, for it is universally agreed that there is no hard and fast line between the two, but a distinction is rather to be sought in the life-cycle involving the alternation of sexual and asexual phases. The protozoa must be recognized as organisms of a higher grade than the bacteria, with more varied conditions of life, greater complexity of functions, and probably with a more variable vitality. Strictly speaking there is no one type of protozoa, the thousands of species which have been named and described being grouped by zoölogists into four great divisions, *sarcodina*, *mastigophora*, *infusoria* and *sporozoa*.

The *sarcodina*, including about 5,500 known and described species, are characterized by changeable protoplasmic processes, called pseudopodia. The great majority are marine or salt water forms and have played an important part in the formation of the earth's crust through the deposition of their calcareous or silicious shells and skeletons.

The *mastigophora*, including those forms which move by one or a few undulating processes called flagella, are the closest protozoan allies to the bacteria, and also, through their colonial forms, to the metazoa. Numerically they are much less important than the preceding class, having less than 500 species, but economically they are rapidly assuming a first importance, and diseases like trypanosomiasis in man and domestic animals, and syphilis, are due to flagellates.

The *infusoria* are characterized by numerous fine cilia, distinguished from flagella by their greater number, shorter length and sweeping stroke. The class comprises the most highly differentiated types of protozoa and includes about 600 or 700 species, among which are several families of highly modified infusoria in which the cilia are replaced in the adult by suckorial tentacles (suctoria). So far as known, these higher types are never pathogenic.

The *sporozoa*, finally, have no motile organs and are invariably parasitic. Their name comes from the characteristic method of reproduction, by sporulation. This group, more than any of the others, has a practical interest inasmuch as a number of diseases in man, as well as in the lower animals, can be traced to them. It is not particularly rich in species, about 250 to 300 being known.

Were we to select a single cause for the origin of the many variations of structure in protozoa, it might well be the adaptations brought about by the various methods of food-getting due to the varied conditions of life. Many, like amœba and its allies, take only living food which is captured by the pseudopodia and digested in internal cavities termed gastric vacuoles; others, like some mastigophora and infusoria, capture their prey by whirlpool currents caused by flagella or cilia; some, like certain ciliates, capture it by specialized harpooning organs, the trichocysts; others, like certain flagellates and sporozoa, have no food-procuring organs, but (like bacteria) living in a nutrient medium, absorb it directly without gastric digestion; still others, like suctoria, procure it through special sucking tentacles, and others, finally, like the phytoflagellates, manufacture their food through the agency of chlorophyl.

Although many protozoa are parasitic—one group, the sporozoa, invariably so—they form a small minority in the total number of protozoa. Some of these parasites are comparatively harmless (gregarines); others, like the pébrine organisms of silk worms, or epithelial-cell parasites of various animals, are extremely harmful. The majority are restricted to a particular organ or tissue; *i. e.*, are limited to a particular kind of food; thus the organisms of smallpox and of scarlet fever thrive in skin cells, the organisms of malaria and of trypanosomiasis, of Texas fever and east coast fever, etc., in the blood; coccidia, in epithelial cells, eimeria salamandræ and cyclospora karyolytica, in cell nuclei, and myxosporidia and sarcosporidia in muscle cells. It is not improbable that this apparent selection is due to chemical or physical actions which the organisms have no power to control, any more than some free-living forms have power to

control the selection of a certain kind of food from abundance of different kinds. For example, *actinobolus radians*, found in pond water, gives no reaction to the impact of hundreds of minute creatures bumping against it, until a particular form, *halteria grandinella*, approaches, when trichocyst-bearing tentacles are shot out, paralyzing the halteria, which is then swallowed. This may be explained as a chemical or physical action which neither organism apparently, has the power to regulate.

The protozoa have the usual physiological animal activities; proteids are digested through the agency of a mineral acid, and undigested food is voided, in many cases through definite and permanent anal openings. The waste products of protoplasmic combustion are thrown off in many cases by definite organs, the contractile vacuoles, although more often by osmosis. They respond in varying degrees to stimuli—some manifesting complex motor reactions, as definite in purpose apparently as any reflex action, others responding sluggishly. Finally, in self-reproduction, the protozoa are exceeded in rapidity only by bacteria, and every conceivable mode of reproduction is met with from slow, equal, binary fission, to prolific multiple fragmentation. The processes of reproduction are governed directly by the food supply, and indirectly by the condition of that complex of functional activities which will be spoken of subsequently as vitality, this varying with the different phases of the life-cycle. The ordinary methods of reproduction are simple or binary division, budding or gemmule-formation, and spore-formation.

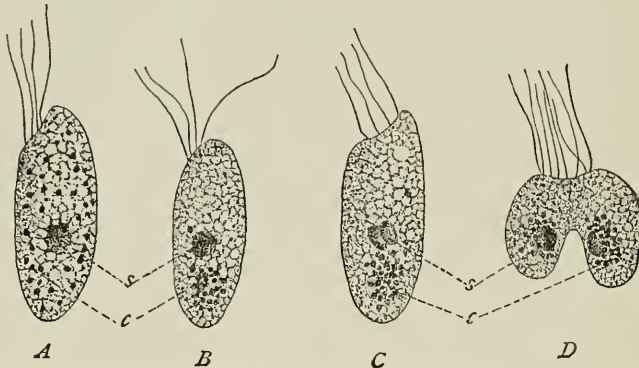
Methods of Reproduction.—Under proper physical and vital conditions, multiplication of the protozoa is very rapid. If certain salts are present, protozoa in a short time may develop in the purest drinking waters to such an extent that, owing to odor and taste, it is unfit for use. If prey is abundant, the same rapid multiplication will take place in all kinds of predatory forms, while parasitic forms are kept down only by the natural immunity of their hosts, by remedial measures, or by loss of their own vitality.

The primary method of increase is that of all cells—simple division—but here, as in all other living things, the number of progeny varies with the difficulties in perpetuating the species. Thus in parasitic forms like sporozoa, simple division has been replaced by the far more prolific method of spore-formation, while the same end is attained in some types by budding or gemmation.

1. Binary Fission.—The process of division in a protozoön is not very different from that in a tissue cell. The nucleus is the first to divide, and then the cell body. Very often there is a complicated nuclear figure consisting of centrosomes, spindle-fibers and chromosomes, but more often the material of spindle fibers and centrosome is compressed into a single intranuclear body called the division-centre, about which the chromatin is massed. Nuclei of this type are called "centronuclei" or "amphinuclei" and these are probably the most typical of all protozoan nuclei. There are many modifications, especially in the primitive forms, the most important being the absence of nuclear membranes and the diffusion of the chromatin granules (chromidium) throughout the cell (*e.g.*, *tetramitus*, Fig. 5). In such cases the granules are collected about the division centre prior to division, and at this period the nuclear elements appear like a typical centronucleus. This "distributed" condition of the chromatin

is also characteristic of the bacteria and possibly represents a phylogenetic stage which is present at some period in the life-history of every known protozoön. The division-centre frequently plays other roles in the cell—thus, in heliozoa it may be the centre of the radiating axial filaments which

FIG. 5.



Division of *Tetramitus Chilomonas* Calkins.—The ordinary vegetative form (A) has nuclear material (c) scattered throughout the cell (distributed nucleus). When preparing for division these granules are grouped in the vicinity of the division centre (B) which divides first (C) after which the chromatin granules are separated into two similar groups about the two parts of the division centre (D).

support the pseudopodia, while in trypanosoma it becomes the “blepharoplast” or main part of the “micronucleus,” and furnishes the substance of the vibratile flagellum.

2. Budding and Gemmation.—In many forms of protozoa, division is frequently asymmetrical, resulting in dissimilar products. Such division may be multiple, forming three or more smaller organisms, and is distinguished from simple, binary fission by the terms budding or gemmation. The budding area, as in the free-living heliozoön, *acanthocystis*, or in the fish parasite, *myxidium*, may be the entire periphery, or as in *acineta* it may be confined to a limited part of the surface. A further complication may be brought about by the insinking of the budding area into the body substance so that the buds are contained in a kind of brood sac. These are distinguished as ectogenous and endogenous budding; the latter is characteristic of the group *myxosporidia* to which some of the most malignant types of animal parasites belong. Here the localized budding areas are called “pansporoblasts” and, as in typical brood pouches, the spores are formed while the animal continues the ordinary vegetative life.¹

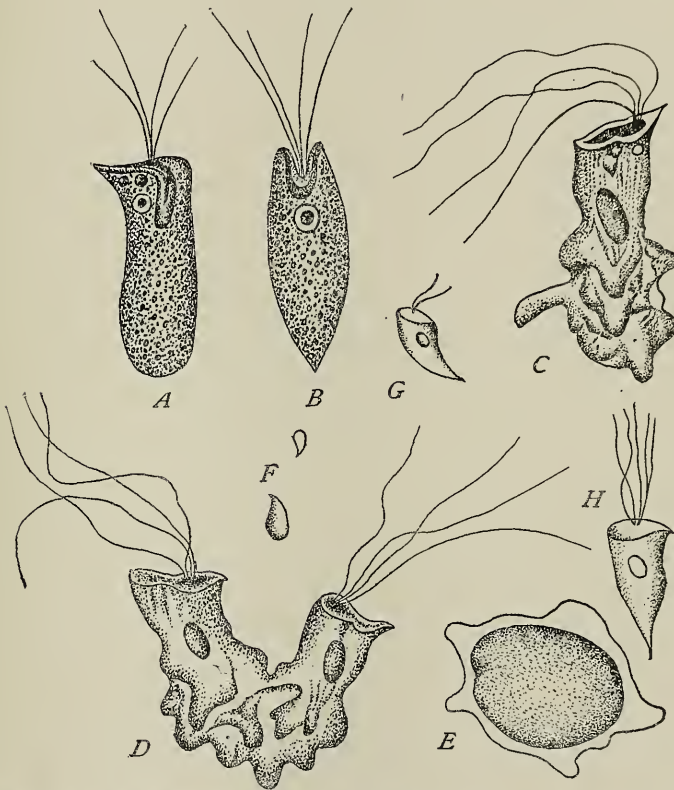
3. Spore Formation.—In some free-living forms, reproduction by division takes place while the animal is protected by a cyst. Thus in *colpidium*, an infusorian abounding in stagnant waters, the cell secretes a cyst, within which it divides twice consecutively, forming four daughter

¹In some types the entire organism forms the pansporoblast, and these have been interpreted by Stempel and Minchin as representing the pansporoblast areas of adult organisms which, in the course of phylogenetic development, have become free and now develop directly into pansporoblasts. This is the type, for example, in the genera *Thelohania*, *Pleistophora*, and *Gurleya*.

individuals. Except in point of numbers this process of reproduction differs in no wise from that known as spore formation, whereby the single cell divides either serially or at one time into hundreds of daughter individuals.

Much confusion has arisen because of a mixed terminology, especially in the case of parasitic protozoa. Consistent terms seem to be sifting out, however, from the heterogeneous collection, and these, based apparently upon natural lines, will probably supplant all others. Schaudinn, whose genius has dominated all lines of protozoan investigation, suggested in

FIG. 6.



Different stages of the Flagellate *Tetramitus Rostratus* Perty. (Stein.)—Ordinary vegetative individuals (A. B. from side and front) reproduce asexually by longitudinal division. They ultimately become plastic (C) and miscible, and two individuals upon meeting (D) fuse. The copula secretes a membrane, and its protoplasm fragments into hundreds of spores, (E) which quickly grow into the parent type. (F. G. H.)

1899 that a consistent terminology of spore-forms is offered by the words "sporoblast," "sporozoite," and "merozoite," and by the words "sporont" and "schizont" which designate the adult forms producing sporozoites and merozoites respectively.

Merozoites and sporozoites indicate biological conditions which are traceable to the general vitality of the parent forms, conditions which

appear not only in parasitic forms but apparently in all protozoa. After a certain number of reproductions by asexual merozoite formation, vitality is exhausted and conjugation, or the union of gametes, takes place, renewing vitality and resulting in spores and sporozoites, produced when the vitality is at its maximum. The sporozoites in turn develop into schizonts, completing the cycle. A simple illustration is afforded by the reproductive phases of certain mastigophora such as *tetramitus* or *cercomonas* (Fig. 6). Here in both cases the usual mode of reproduction is by simple longitudinal division, the daughter cells being equivalent to merozoites. After division has been repeated for many generations, the organisms lose their definite contour, become plastic, and two of them upon meeting, fuse to form a fertilized cell, the copula. Within the copula wall, the protoplasm breaks up into hundreds of reproductive bodies equivalent to sporozoites, but to which the name "spore" has been applied for many years.

Turning from these simple cases to the complicated but analogous reproduction of sporozoa, we find that the same principle holds good, and "spore" products are formed after sexual union. Confusion has arisen because the asexual reproduction, which in *tetramitus* takes place by binary fission, is replaced in sporozoa by the more prolific multiple division or spore-formation in the old sense. The reproductive elements, which are formed in this way, are termed merozoites to distinguish them from the reproductive bodies formed after conjugation, while the process by which they are formed is termed schizogony, and the producing adult, the schizont. After this asexual method has been repeated for a more or less definite period, merozoites are formed which develop into conjugating individuals termed gametes, which like *tetramitus*, may be similar to one another, or, unlike *tetramitus*, may be sexually differentiated. If the latter, the larger, yolk-stored quiescent forms are the macrogametes, the minute, actively motile, spermatozoa-like forms, are the microgametes. After union of the sexual elements, the encysted copula becomes either a single sporoblast, or it divides into from two to many parts, each one being a sporoblast. Each sporoblast may be separated from the others by a special sporocyst (as in coccidia), or the sporoblasts may be merely reproducing centres without special sporocysts (as in plasmodium and *laverania*), but in all cases the sporoblasts give rise to the ultimate reproductive bodies or sporozoites which, usually protected by spore-capsules, are shielded from the exigencies of a more or less prolonged ectogenous cycle.

Spores in the myxosporidia differ from those in other protozoa in having one or more specialized thread-holding capsules. These so-called "polar capsules" are sufficiently characteristic to distinguish the spores of myxosporidia from all other sporozoan reproductive bodies. The function of the thread is to assist the sporozoite in securing attachment to epithelial cells when taken into the digestive tract of a new host.

The variations which occur in the different types of sporulation in sporozoa are legion; among these *monocystis ascidiæ* is noteworthy in having two adult organisms (sporonts) unite to form a common cyst (Fig. 7). Each divides into a number of amœboid elements, the gametes, which fuse two by two (in the allied genus *stylorhynchus* the conjugating gametes come from different cells and this is presumably true of *monocystis*). Each of the many copulæ forms a single sporoblast and

gives rise to eight sporozoites. Another variation is seen among the coccidia where in some cases, (adelea, cyclospora, etc.), the ultimate sexually differentiated gametes are represented by a long series of generations of sexually differentiated merozoites.

FIG. 7.



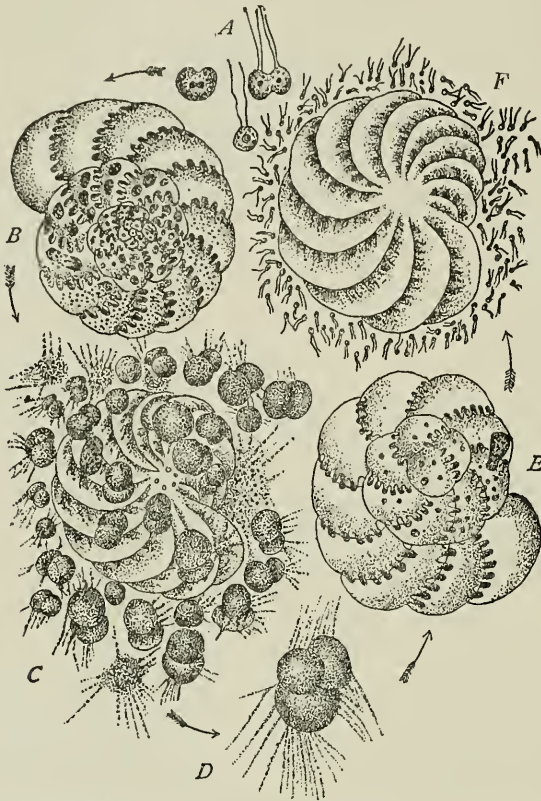
Life Cycle of *Monocystis Ascidiæ*. (Siedlecki.)—The young sporozoites enter epithelial cells (A, B, C), and grow into adult gregarines which leave the cells (D), and live as "sporonts" in the cavity of the intestine. Two sporonts unite (E), their nuclei divide repeatedly (F), until many daughter-nuclei are formed (G). These become nuclei of amoeboid gametes (H), which move about inside of the cyst, and soon conjugate two by two (I), the nuclei fusing to form cleavage nuclei of the sporoblasts (J). The cleavage nuclei then divide thrice to form eight daughter-nuclei (K, L, M, N), which ultimately become nuclei of the sporozoites (O). The sporoblasts, meanwhile, secrete firm cysts within which the sporozoites are protected.

The merozoites do not leave the host, but migrate to new localities where they repeat the process of development and sporulation, until they ultimately change into the sexually differentiated reproductive bodies; these, after fertilization, produce the cyst-protected sporozoites, which remain quiescent until carried into new hosts. Merozoites thus give rise to auto-infection of the host, and sporozoites to fresh infection of new hosts, most frequently by way of the digestive tract where they are carried with the food. The cysts are then dissolved off by the gastric fluids, and the liberated sporozoites make their way into the epithelial cells. In appearance they closely resemble the merozoites but can be usually distinguished by minor differences such as general contour, presence of pigment, nuclear characteristics, or other features.

In non-parasitic protozoa we meet with closely similar life-cycles having the same alternation of sexually and asexually produced spores. In

marine foraminifera, for example (polystomella, Fig. 8), the alternation is shown by structural differences in the adult shells and in the reproductive elements. Shells that are formed by recently fertilized gametes (equivalent to developing sporozoites) have a small central

FIG. 8.



Life cycle of *Polystomella Crispa S.* (Lang and Schaudinn.)—A young form derived from the union of two flagellated gametes (A) develops into an organism with microsphaeric type of shell. The nucleus increases by mitosis until many nuclei are present when they break up into granules of chromatin (B). The protoplasm fragments into reproductive bodies, equivalent to merozoites (C), each having several granules of the distributed chromatin ("Chromidien"). Each reproductive body (D) develops into an adult with a macrosphaeric type of shell, and with nuclei in the form of small chromatin granules (E). When mature these forms fragment into hundreds of flagellate gametes (F) which conjugate, and so complete the cycle.

chamber (microsphaeric). The adult reproduces by amœboid spores (pseudopodiospores), equivalent to merozoites, which grow directly into shelled organisms with comparatively large central chambers (macrosphaeric). These ultimately produce flagellated swarm spores (flagellispores or gametes) which conjugate and so complete the cycle.

The universality of these alternating generations indicates that we have to do with a fundamental biological phenomenon of the utmost importance.

Recent research has given a hint that the secret may lie in the varying conditions of vitality at different phases of the cell-cycle. A protozoön begins life after conjugation, with a certain potential of vitality which is gradually used up in the continued vegetative activities and by asexual multiplication. With advancing age and decreasing vitality protoplasmic changes occur which indicate the approach of renewed sexual activity. This sequence of changes is known as the life-cycle.

The Life-cycle.—Modern research on protozoa emphasizes the fact that study of a single individual or of a group of individuals in the same stage of their life-cycle, fails to give an adequate conception of the species to which they belong. The significance of this is evident when it is recalled that recently it has been claimed that certain species of the genus *halteridium* and certain species of *trypanosoma* are phases of the same organism, or that certain species of *pelomyxa* are but stages in the life-history of *amoeba*. Earlier evidence of the same confusion was shown by the *polymitus* form which was later identified as the sexual stage of malarial organisms. It is certainly reasonable to expect that further research on life-cycles will prove that of the 7,000 species of protozoa now on record, many are but form-changes of the same organisms.

The facts which have been obtained from the study of a few life-histories indicate that these form-changes are expressions of a varying vitality, and even more important than this, they indicate that the general biological laws which we recognize in the development of higher animals and plants are equally applicable to protozoa. We now know, for example, that the changes are characteristic of periods in the life-history which compare with the metazoan periods of youth, adolescence, and old age. We know that natural death from protoplasmic old age is as inevitable in protozoa as in metazoa provided conjugation is prevented, and we have strong evidence, though as yet no actual proof, that conjugation, the analogue of fertilization, is not a specific process of reproduction, but a process of rejuvenescence, through which a weakened vitality is restored to full activity.

These points may be illustrated by the comparatively simple life-history of a free-living form like *paramoecium*, the "slipper-animalcule." A single individual was isolated and placed in water that had been boiled with hay; on the following day the *paramoecium* had divided twice and the four individuals were each isolated in hay infusion as before. The four lines thus started were kept separate and daily isolations were made for a period of twenty-three months, and until the original protoplasm had divided 742 times. The accompanying diagram shows the variations in vitality during the entire period, the number of generations for all four lines being averaged in ten-day periods. After about 200 generations the vitality of the race sank to such a low point that the majority died and the rest were saved only by substituting, for a few days, a meat extract in place of the hay infusion. The result was a vigorous renewal of vitality lasting for approximately 200 generations more, when a second period of depression set in (see first and second cycles of diagram). Again some were saved by a change of diet, and others by adding salts to the hay infusions (potassium phosphate). This resulted in a third cycle of generations which again ran out, this time at the end of 193 generations (see

FIG. 9

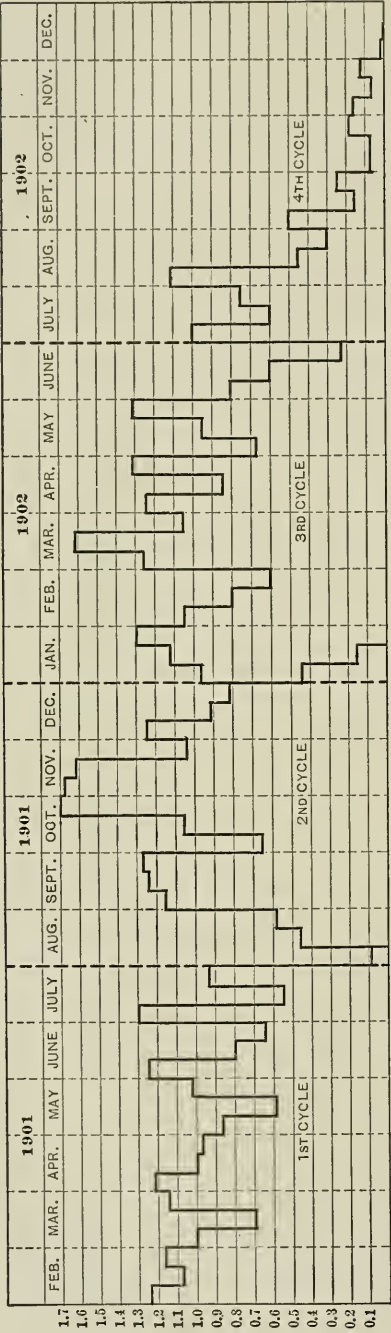


Diagram representing the life cycles of *Paramoecium Caudatum*.—The numbers of divisions per day for all individuals of the race under observation, were averaged in ten-day periods, thus giving a convenient means of comparing the vitality at different times. The first cycle ended in July, 1901, the organisms being stimulated with beef extract. The second cycle, thus artificially started, ended in January, 1902. The line in the diagram carried to the base indicates that half of the organisms which were kept on the hay infusion as control, all died, while the rest which were given beef-extract or simple salts, were restimulated and started on the third cycle which ended in June, 1902. Half were again stimulated artificially, this time by extracts of pancreas and of brain, but all died out in December, 1902, the last ones in the 742nd generation. In the second and third cycle, the periods of sexual activity were from November to January, and from April until June, while in the last cycle the organisms would not conjugate at all.

third cycle of diagram). This time there was more difficulty in saving the race but they were finally rejuvenated by using extracts of pancreas and of brain. The resulting cycle was weak however, and after 126 generations the entire race died from unmistakable old age.

There is no doubt that the race would have died from what might be called old age in any one of the three periods of depression, had not stimulants in the form of dissolved salts been used. The effect produced by these salts was exactly the same as that produced in artificial parthenogenesis in egg cells, and apparently, the same as that produced in conjugation. With the exception of the last, each cycle (approximately of 200 generations) represents a complete life-cycle in which can be distinguished periods of vigor, sexual activity and senescence (Fig. 9). It is in the period of sexual activity which begins near the culminating point of the life-cycle curve, that changes in the protoplasmic composition become apparent. The cell body becomes plastic, and miscible—a physical state well adapted for conjugation—and two or more organisms, coming in contact at this period, will unite. In the later period of senescence the various organs of the body become degenerated, cell division is imperfect, and monsters are frequently formed,—all evidences of exhaustion.

The life-cycle of paramœcium shows evidence, therefore, of variations of vitality which correspond with periods of youth, adolescence, and old age in metazoa. During these several periods the protoplasm undergoes distinct structural changes, evidenced in the second phase by a miscible condition during which conjugation is possible. If conjugation is prevented the ordinary metabolic processes come to an end and the organisms die. Their protoplasmic structure at this time indicates that the metabolic processes have reached a state of stable equilibrium from which they may be stimulated to renewed activity by artificial means. Ultimately, however, such artificial measures as change of diet, salts, etc., are ineffectual, and, although the experiments indicated that the digestive processes were renewed, the results showed that something—a something which may be called the dividing energy—had become exhausted and the last of the race of paramœcium died. There is reason to believe that conjugation results in a new chemical organization of the nuclei, and with this, a renewal of the processes of division, of digestion, and of other functions, so that immediately after conjugation, if this supposition is correct, we should expect the most vigorous activity.

Turning now to other protozoön-cycles, we find similar phenomena, intelligible in the light of these experiments; thus in the flagellates, *Tetramitus* and *Cercomonas*, after a period of increase by division, the regular contour of the body is lost, the individuals become plastic and, while in this condition, conjugate and form their spores (Fig. 6). The change in protoplasmic structure is an indication of a period in the life-cycle equivalent to that of paramœcium, in which the miscible state is predominant. In some forms this period of the life-cycle results in the formation of different sizes of individuals of which the large ones remain fixed and quiescent (female), while the small ones are migratory (male) and fuse with the larger ones. This size-difference may become exaggerated to such an extent in coccidia and hæmosporidia, that the equivalent of metazoön eggs and spermatozoa result. This physiological condition of the organism, therefore, is apparently the signal for the

development of sexually differentiated individuals, a view which Minot expressed in 1879 in the statement: "The exhaustion of the rejuvenating power becomes the stimulus for the formation of the sexual products."

Not only is the cell-body altered in composition but, in many forms, the structure of the nucleus is likewise changed. In rhizopods like *amoeba*, *arcella*, *centropyxis*, etc., and in foraminifera and sporozoa, a quantity of chromatin is given off from the nucleus in the form of granules which lie distributed throughout the cytoplasm, unconfined by a nuclear membrane, a condition exactly comparable with the distributed nucleus of *tetramitus* or of bacteria. These granules were called the "Chromidien" by Hertwig, while Schaudinn, with others, has shown that they form the minute nuclei of the sexually differentiated individuals. These nuclear processes are well illustrated in the life-cycle of the foraminiferon, *polytomella*, which, as stated above, has a many-chambered calcareous shell occurring in two forms, one with a large central chamber, the other with the corresponding chamber much smaller. The explanation of this size-difference was the key to the life-history of these foraminifera. The nuclei of the small-chambered individuals break up into countless fragments, the "Chromidien," (or chromidium) which are ultimately distributed to small *amœboid* fragments of the parent organism formed by a process analogous to merozoite formation in coccidia. These *amœboid* spores develop into adult organisms with the large-chambered shell in which the distributed chromatin granules become the minute nuclei of small flagellated gametes which swarm out from the parent shell. Two of these gametes from different parents upon coming together conjugate, and the copula develops into an organism with a minute central chamber. In this organism when grown, the distributed nucleus is again ultimately formed in preparation for future conjugations (Fig. 8).

Another life-history worked out by Siedlecki, and offering some variations upon the above, is that of a parasitic gregarine living in the cavities of a salt water ascidian (Fig. 7). Here the distributed chromatin is formed by repeated divisions of the nucleus. The young parasite in the sporozoite stage enters an epithelial cell of the gut and develops into the adult gregarine. It becomes free in the lumen of the intestine and is soon joined by a second. They secrete a common cyst in which the nucleus of each individual divides many times, forming two multinucleate cells. Each cell then divides into as many minute parts as there are nuclei. A large number of *amœboid* gametes are formed, those from one of the conjoint animals fusing with those from the other. After this union of the gametes each copula becomes a sporoblast and secretes a capsule in which the spore contents divides into eight parts, the sporozoites. The latter are retained and protected within the spore-cysts until eaten by some new host when the cyst walls are dissolved by the digestive fluids, and the sporozoites are liberated.

A still more complicated process is shown by the epithelial cell-parasite, *coccidium schubergi*, described by Schaudinn (Fig. 10). Here the sporozoite enters an epithelial cell, grows to adult size, leaves the cell and forms merozoites by repeated divisions of the nucleus and of the cell-body. The merozoites repeat the cycle and new merozoites are formed again and again. Ultimately the merozoites develop into sexually-

differentiated forms which produce macro- and microgametes, the nuclei of the microgametes being formed from the granules of the "Chromidien." These gametes unite and each copula secretes a protecting covering and forms four sporoblasts. In each sporoblast, two sporozoites are pro-

FIG. 10.



Life cycle of *Coccidium Schubergi*. (After Schaudinn.)—Sporozoites penetrate epithelial cells, and grow into adult intracellular parasites (*a*). When mature, the nucleus divides repeatedly (*b*); and each of its sub-divisions becomes the nucleus of a merozoite (*c*). These enter new epithelial cells, and the cycle is repeated many times. After five or six days of incubation, the merozoites develop into sexually differentiated gametes; some are large and well stored with yolk material (*d*, *e*, *f*); others have nuclei which fragment into many small particles ("Chromidien") each granule becoming the nucleus of a microgamete or male cell (*d*, *h*, *i*, *j*); The macrogamete is fertilized by one microgamete (*g*), and the copula immediately secretes a fertilization membrane which hardens into a cyst. The cleavage nucleus divides twice, and each of the four daughter-nuclei forms a sporoblast (*k*) in which two sporozoites are produced (*l*).

duced which are protected by spore-cases and by the parent sporocyst, until the walls are dissolved and the sporozoites are liberated to repeat the cycle.

Other, and even more complicated life-cycles in cyclospora, arcella, centropyxis, etc., might be cited, but they all agree in essential features with the examples given.

Turning now to the malignant protozoa which are supposed to be the causes of certain human diseases, we find, for the most part, only disconnected portions of life-cycles. With the exception of the malaria organ-

isms, the complete life-history of not one disease-causing form is known. We are completely in the dark concerning the causes of many of the exanthematous diseases, yellow fever and cancer, and of some of these we cannot say, even, that the causes are parasites and still less can we affirm that the parasites are protozoa. Even in diseases that are known to be due to protozoa much remains to be done before the life-histories are complete. *Trypanosoma*, being a saprophytic type and therefore capable of cultivation, offers especial advantages for study, but even with these, little more than the schizogony is known. The recent preliminary account which Schaudinn published, according to which the life-cycle of *trypanosoma* involves a change of hosts, and an alternation of intracellular and extracellular habitats, cannot be accepted without further evidence. The same uncertainty exists in regard to the cycle of *cytorhyctes variola*, where, according to the tentative life-history a cytoplasmic phase and a nuclear phase characterize the asexual and sexual processes, respectively. No certainty can attach to such a life-history until the organism can be followed from its first invasion of the human host to its last spore-stage. *Cyclasterella* (*Cyclaster*) *scarlatinialis*, the organism found by Mallory in skin cells of scarlet fever patients, has been seen only in its vegetative and merozoite stages. *Piroplasma* (*Babesia*) *hominis*, described by Wilson and Chowning as the cause of tick fever, is known in only one phase, while even the allied and better known *piroplasma bigeminum* (*Babesia bovis*) of cattle, must still be studied for its sexual phases and sporogony. *Entamoeba histolytica*, which, according to Schaudinn is the malignant amoeba of tropical dysentery, has been followed through its schizogony and as far as the development of the "Chromidien," while *entamoeba coli* (*amoeba coli* syn.), a harmless commensal in the human intestine has been followed only through schizogony. *Spirochaeta* of syphilis is known in only one phase, and analogy alone suggests that this organism, too, has a complex life-cycle.

On the whole, we are compelled to state in regard to pathogenic protozoa in man that, up to the present time, little more has been done than to break ground in an extremely difficult field of research, and that, deprived for the most part of the possibility of experimentation, and relying merely upon morphology, future progress must necessarily be slow. We are in a position, however, to draw some positive conclusions from pure morphology. Enough is known to show that more or less definite structural characteristics accompany the three general periods of a protozoan life cycle. The youthful organism is characterized by marked conformity to type; the older organism in the period of adolescence, by well marked nuclear changes, by chromidium formation and by physical changes in the cytoplasm; while old age is signalized by vacuolar degeneration and decreased size. The value of these morphological characteristics is shown by A. W. Williams' discovery of a definite chromidium in the Negri bodies. This chromidium being of the same type, and having a history similar to that in *Orcella* or *Centropyscis* enables us to classify these organisms of rabies as rhizopods.

The importance of the sexual phase in the life-history of protozoa is unmistakable, but its significance has been variously interpreted. Some observers include phenomena of conjugation with those of egg fertiliza-

tion and agree with Darwin, Spencer, O. Hertwig, Hantschek and others, that the process has as its primary object the prevention of indefinite variation, and tends to keep the species true to its type. Others, like Brooks and Weismann, have maintained an opposite view, that sexual union has been developed as a method of originating variations; still others agree with Bütschli, Minot, Jensen and Maupas, that conjugation, like fertilization of the egg, involves a process of rejuvenation, whereby the cell is stimulated to renewed activity. The experimental evidence supports the latter hypothesis. While Weismann, on an *a priori* basis, maintained that protozoa are too simply organized to die a natural death from old age, Maupas' experiments, confirmed by later researches, demonstrated the opposite. "Senescence," Maupas says, "appears to be a very general phenomenon, at least in the animal kingdom. . . . It is inherent in the organism and comes from internal causes which act independently of the surrounding conditions. . . . Its deleterious action is offset and annulled by sexual rejuvenescence or conjugation."

In the experiments with paramœcium, referred to above, it was demonstrated that, like sea-urchin eggs artificially fertilized, senescent protozoa can be re-invigorated by stimuli,—in paramœcium by potassium phosphate and the salts of meat extract; but it was also demonstrated that these stimuli have no permanent effect, and that the organisms ultimately die of old age. In some forms of protozoa, although not in paramœcium, similar physiological exhaustion apparently does not result in death of the organisms, but leads to the formation of protecting cysts, within which the living cells remain quiescent for varying periods, until environmental conditions are favorable to liberation and renewed activity.

Experiments upon free-living forms, especially upon flagellated types, have shown that changes in density of the surrounding medium produce these physiological conditions necessary to gamete-formation, and sexual, conjugating elements are formed.

Applying these general principles to pathogenic protozoa, we note that the experiments involving changes of density of the surrounding medium are reproduced in nature in the life-history of the blood-dwelling malaria organisms, when sexual elements are developed upon exposure to lowered temperature of the air, or to the cold environment of a mosquito's gut. Again, from these general principles, it is reasonable to expect that, if prevented from conjugating, the virulence of a specific form should gradually decrease until the disease runs itself out. We should expect in a malaria infection, for example, that the organisms would be less susceptible to drugs at the outset than later when their vitality is reduced, and that, ultimately, they would die out from functional degeneration, subject to the possibility, however, of encystment and artificial stimulation through some minute change in chemical composition of the host's blood. This principle is illustrated in the life-history of the trypanosoma of the owl, where, according to Schaudinn's descriptions, one of the types, called by him the "indifferent form," is capable of parthenogenetic development within the host, and of reproducing the disease. It is illustrated again in the history of the Texas fever organism, piroplasma bigeminum, where the hæmatozoa apparently lose their dividing energy, and remain latent in the blood for indefinite periods, and still again in human malaria where the plasmodium may remain latent, sometimes for many years

CLASSIFICATION.

SUB-KINGDOM. *Protozoa*.—Unicellular animal organisms which reproduce by division or spore-formation; solitary or united in colonies; free-living or parasitic.

PHYLUM I. *Sarcodina*.—Protozoa with changeable protoplasmic processes or pseudopodia.

CLASS I. *Rhizopoda*.—Sarcodina with pseudopodia in the form of lobose or reticulate processes; with or without shells.

SUB-CLASS. *Amabida*.—Pseudopodia lobose.

ORDER 1. *Gymnamabida*.—Naked amœboid forms with lobose pseudopodia. Here are placed a few parasitic forms belonging to the genera *Amœba*, *Entamœba*, and *Leydenia*.

ORDER 2. *Thecamabida*.—Shell-bearing amœboid forms with lobose pseudopodia; no parasitic form.

SUB-CLASS. *Foraminifera*.—Divided into 10 orders; the various genera are salt water forms for the most part, and are never parasitic.

(Sub-class *Mycetozoa* would be placed here were we to consider these forms as protozoa instead of fungi. Here are placed parasitic forms such as *Plasmodiophora*, *Tetramyxa*, *Labyrinthula* and other parasites of plants.)

CLASS II. *Heliozoa*.—The genera are confined mainly to fresh water and are never parasitic. They are sub-divided into four orders according to the nature of the skeleton.

CLASS III. *Radiolaria*.—Salt-water forms of protozoa, never parasitic.

PHYLUM II. *Mastigophora*.—Protozoa with flagella.

CLASS I. *Flagellata*.—Small forms with from one to several flagella; with a strong tendency to form colonies.

ORDER 1. *Monadida*.—Minute forms with from one to three flagella. There is no definite mouth-opening and nutrition is holozoic, saprophytic, or parasitic. The parasites and commensals which belong to this order are species belonging to the genera *Cercomonas*, *Herpetomonas* and *Trypanosoma*.

ORDER 2. *Choanoflagellida*.—With collar-like processes surrounding the base of the flagellum; not parasitic.

ORDER 3. *Heteromastigida*.—With two or more flagella of dissimilar length; the genus *Bodo* is parasitic.

ORDER 4. *Polymastigida*.—The flagella are numerous and of similar or dissimilar size. Here are several ecto- and endo-parasitic forms belonging to the genera: *Costia*, *Tetramitus*, *Trichomonas*, *Monocercomonas*, *Hexamitus*, *Lambliia*, *Polymastix*, *Lophomonas*, *Trichonympha*, *Pyrsonympha* and *Joenia*.

ORDER 5. *Euglenida*.—No parasites.

ORDER 6. *Phytoflagellida*.—Flagellates with coloring matter in the form of green, yellow, or brown chromatophores. Frequently colonial. Here belong the most frequent sources of odors in drinking waters, the following genera being especially noteworthy: *Dinobryon*, *Synura*, and *Uroglena*, all colonial forms, with yellow chromatophores.

ORDER 7. *Silicoflagellida*.—A single genus of salt water mastigophora with latticed skeleton. *Distephanus*, parasitic on radiolaria.

CLASS II. *Dinoflagellata*.—Never parasitic.

CLASS III. *Cystoflagellata*.—Two genera of characteristic form. One, *Noctiluca*, is remarkable for the vivid phosphorescence which it causes.

PHYLUM III. *Infusoria*.—Protozoa with cilia. In the sub-phylum ciliata these are present at all times; in the sub-phylum suctorina they are present only during the young or embryonic phases.

ORDER 1. *Holotrichida*.—The cilia are distributed over the surface, and there is no specialized oral apparatus known as the “adoral zone” consisting of cilia fused into “membranelles.” Here are found some parasites belonging to the genera *Ichthiophthirius*, *Butschlia*, *Anophrys*, *Isotricha*, *Dasytricha*, *Opalina*.

ORDER 2. *Heterotrichida*.—With cilia distributed over the general surface and, in addition, a specialized adoral zone in the mouth region. Here are several well-known parasitic forms belonging to the genera *Nyctotherus*, *Balantidium*, *Entodinium*, *Diplodinium*, *Ophryosecolex* and *Cycloposthium*.

ORDER 3. *Hypotrichida*.—The cilia are limited to the ventral surface, and are frequently fused into specialized organs of motion and touch, the cirri. There are no strictly parasitic forms.

ORDER 4. *Peritrichida*.—The cilia are greatly reduced, in some cases to the adoral zone, but additional rings may be present. Several ectoparasites belong here, especially the genera, *Spirochona*, *Kentrochona*, *Lichnophora*, *Cyclochaeta* and *Trichodina*.

SUB-CLASS. *Suctorioria*.—Infusoria with suctorial tentacles in the place of cilia. They are frequently ectoparasites and the young of some genera, *e.g.*, *Sphærophrya* are internal parasites in other infusoria.

PHYLUM IV. *Sporozoa*.—Protozoa without motile organs; reproduction by sporulation; always parasites.

CLASS I. *Telosporidia*.—Sporozoa in which the act of reproduction ends the individual's life, the entire protoplasm being used in forming spores.

ORDER 1. *Gregarinida*.—The young stages alone are cell parasites, the adult organisms living in fluids within the cavities of animal hosts. There are no human parasites.

ORDER 2. *Coccidia*.—Intra-cellular parasites, mainly in the epithelial cells of vertebrate and invertebrate hosts. Human parasites have been traced mainly to the genus *Coccidium*. Here also we should place *Cyclasterella scarlatinalis* Mallory.

ORDER 3. *Hæmosporidia*.—Sporozoa of small size living in the blood corpuscles of vertebrates. Human parasites belong to the genera *Laverania*, *Plasmodium*, and *Piroplasma*.

CLASS II. *Neosporidia*.—Sporozoa in which the entire cell is not used at one time in forming spores, the latter developing while ordinary vegetative processes are carried on.

ORDER 4. *Myxosporidia*.—Neosporidia with spores containing polar capsules and anchoring threads. Here belong several genera of note, in that serious epidemics of lower animals are caused by them, *e.g.*, *nosema*—causing pébrine disease in silkworms, *Myxobolus*, *Myxidium*, etc.

ORDER 5. *Sarcosporidia*.—Neosporidia in which the initial stages are passed in muscle-cells of vertebrates. Cysts are formed with double membranes in which kidney-shaped reproductive elements are produced. The one genus occasionally parasitic in man is *Sarcocystis*.

This phylum is particularly rich in forms whose affinities are too obscure to permit of taxonomic position, and further work must be done before they can be accurately placed. There is strong evidence that future research will demonstrate the necessity of another class to hold these organisms, or perhaps, several classes. At the present time such forms can only be admitted as *Sporozoa Incertæ Sedis*, and as such we would include the genera *Ophryocystis*, *Serumsporidium*, *Lymphosporidium*, *Blanchardina*, *Cytoryctes* and *Neurocytes*. (It is probable from Williams' observations that *Neurocytes*, the cause of rabies, is a rhizopod and not a sporozoa; if so, *Cytoryctes*, which is closely related, must be placed there too.)

CHAPTER XVIII.

MOSQUITOES.

By L. O. HOWARD, PH.D.

EVERY person interested in human health should have some knowledge of mosquitoes. The carriage of malaria by the different species of the genus *Anopheles* and the transference of yellow fever by *Stegomyia calopus* render it necessary that not only medical practitioners but also the laity should be thoroughly familiar with the characters which distinguish these mosquitoes in order that they may at once be recognized not only in the adult form but in all the stages of their existence. The important discoveries which have been made regarding the carriage of disease by mosquitoes render further discoveries of a similar nature not only possible but rather probable, and therefore information among the medical profession regarding them should be widespread; or at least there should be convenient sources of information for the use of those who wish to go rather deeply into the subject, and which may be available in case of needed emergency investigation. It is for these reasons that considerable space is devoted here to the consideration of mosquitoes, their habits, life history, classification, and methods of control.

So far as is known definitely, the larvæ of all mosquitoes inhabit water, although they are true air-breathers—that is to say, they come to the surface of the water at longer or shorter intervals to breathe.¹

Mosquitoes are rapid breeders, and pass the pupal condition also in the water, but floating normally at the surface. Most species pass through several generations in the course of a summer, and many of them hibernate as adults hidden away under the bark of trees, in protected places like outbuildings, the under side of bridge culverts, in old boxes, and in the cellars and attics of houses. In the extreme southern states many species are active throughout the winter, and even as far north as Washington, mosquitoes in heated houses may bite in December and January. In localities where there are prolonged dry spells and where heavy rains are to be expected only at certain seasons of the year, adult mosquitoes of many species live through the dry spells and lay their eggs as soon as the rains come. This is especially the case in tropical regions where the year is divided into wet and dry seasons. Certain species do not necessarily hibernate as adults or live through the dry seasons as adults. There are many species which may exist for a long time in the egg stage, the eggs being laid in places like small excavations, sure to be filled with water when heavy rains occur, and others hibernate in the larval state.

Under normal summer conditions of temperate regions, when rains occur more or less frequently, the life of the average adult mosquito is

¹The larvæ of *Culex dupreei* and *C. discolor* offer the only known exceptions to this rule

short, and in fact the term of the life of the adult seems to be dependent mainly upon the opportunity of propagation which is the main purpose of the adult. The adult male mosquito does not necessarily take nourishment. It will sip water or any liquid substance, like juices of fruits and even the honey of flowers. The adult female does not necessarily rely upon the blood of warm-blooded animals; they are plant feeders, and very few of the countless millions ever get an opportunity to taste the blood of a warm-blooded animal. They have been seen puncturing the heads of young fish and swarming about turtles when the latter are upon land. They also have been seen puncturing the chrysalis of a butterfly.

The larvæ, on the contrary, feed upon all sorts of minute organisms floating upon the surface, held in suspension in the water, or resting upon the bottom of pools.

Many species are adapted successfully to resist extremely low temperatures. Arctic travelers speak of the abundance and voracity of Arctic mosquitoes. They occur in enormous swarms during the short summers of Alaska, Lapland and Greenland.

Classification.—All mosquitoes belong to the order Diptera, or two-

FIG. 11.



Wing of a mosquito, showing scales. (Original.)

winged flies, and to the family Culicidæ. The species of the family Culicidæ may at once be distinguished from all other dipterous insects by the fact that the wing veins and the body bear flattened scales. There are certain other insects which bear a close general resemblance to true mosquitoes, such as certain crane-flies of the family Tipulidæ, and especially of the genus *Geranomyia* in which the insect has a distinct mosquito-like form and a prolongation of the mouth-parts resembling the mosquito's proboscis, but when examined under a microscope or high power hand-lens the wing veins are seen to be naked—not clothed with scales or hairs.

The family Culicidæ has been divided into several sub-families, but for the purposes of this work it is only necessary to consider the sub-families Culicinæ and Corethrinæ, the former sub-family including all true biting mosquitoes and the latter those forms in which the proboscis is short and not formed for piercing. Certain authors have split up the biting mosquitoes into several sub-families, and have even given some of them family rank. Such a classification seems premature and the families so created do not seem to have equal classificatory rank or to be founded upon as important morphological characters as the other accepted families in the order Diptera. Considering, therefore, all true biting mosquitoes as belonging to the sub-family Culicinæ, the principal North American genera will readily be distinguished by the following table, and the

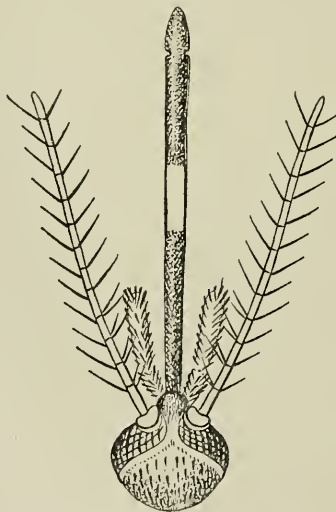
non-biting mosquitoes of the sub-family Corethrinae will receive no further consideration in this account.

Synoptic Table of the Principal Genera of the Biting Mosquitoes (Culicinae) of the United States.

- | | |
|--|----------------------|
| 1. Palpi in the male at least nearly as long as the proboscis; in the female less than one half as long..... | 3 |
| Palpi in both sexes at least almost as long as the proboscis..... | 2 |
| Palpi in both sexes less than one-half as long as the proboscis..... | 7 |
| 2. Proboscis straight or nearly so, colors of body brown and yellowish..... | <i>Anopheles</i> |
| Proboscis very strongly curved, colors bluish or greenish..... | <i>Megarhinus</i> |
| 3. Legs bearing many nearly erect scales..... | <i>Psorophora</i> |
| Legs destitute of such scales..... | 4 |
| 4. Back of head bearing many narrow scales..... | 5 |
| Back of head covered with broad, appressed scales..... | <i>Stegomyia</i> |
| 5. Feet black, the hind ones in part snow-white..... | <i>Janthinosoma</i> |
| Feet not marked like this..... | 6 |
| 6. Scales in outer rows on sides of veins of wings very narrow, scarcely tapering at the base..... | <i>Culex</i> |
| Scales in outer rows on sides of veins in basal half of wings very narrow, many of those in apical half of wings rather broad and distinctly tapering at the base..... | <i>Melanoconion</i> |
| Scales of wings very broad, strongly tapering at the base..... | <i>Teniorhynchus</i> |
| 7. Upper side of thorax with line of bluish scales..... | <i>Uranotania</i> |
| Upper side of thorax not marked in this way..... | 8 |
| 8. With several bristles below the scutellum..... | <i>Wyeomyia</i> |
| Without such bristles..... | <i>Aedes</i> |

Certain additional generic names are used in connection with American mosquitoes, especially *Grabhamia* and *Theobaldia*. Mr. D. W. Coquil-

FIG. 12



Head and beak of a mosquito, showing antennæ, palpi, proboscis. (Original.)

lett, who is responsible for the preceding synoptic table, is not yet quite certain of the status of these two genera. Certain generic names have also been proposed by Felt and by Dyar in which the genera are based upon

examinations of the genitalia of the male sex. While it is quite likely that these genera may be valid, more must be known about them before they are introduced into a work of this character. It may also be stated that just as this article is being completed a West Indian genus, *Deinocerites*, has been taken by Dyar at Miami, Florida. *D. cancer*, the species captured, breeds in brackish water at the bottom of crab holes near the sea.¹

MOSQUITOES OF THE GENUS *CULEX*.

None of the species of the genus *Culex* have been definitely and acceptably shown to be responsible for the carriage of disease in temperate or subtropical regions, although the parasitic worms of the genus *Filaria*, are said to be carried and transmitted by *Culex fatigans* as well as by *Stegomyia calopus* and *Anopheles*. The claim that dengue fever is transmitted by a *Culex* does not seem as yet to have been fully substantiated. The species of this genus may be recognized by the more or less erect forked scales on the head and the slender elongate side scales of the wing veins. Although many genera have been split off from the genus *Culex* as it was understood as late as 1900, by Theobald and other writers, the genus still remains complex and is likely to be still further split up. Although the adults of the genus as at present understood have a comparatively uniform structure and may not readily be divided generically by sound morphological characters, the larvæ differ radically among themselves, and many important points in the life history are so variable among the species as to render a prophecy as to future generic subdivision probably sound. Many of the individual species which are accepted to-day have two or more distinct types of larvæ from which are bred non-separable adults, which would seem to indicate the necessity for new species based on larval characters.

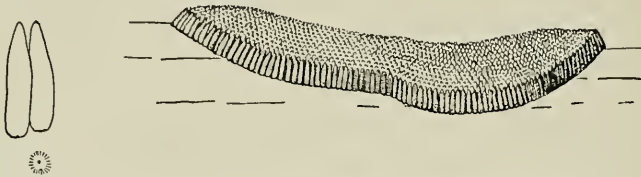
The type of the genus has always been considered to be *Culex pipiens* of Linnæus, an almost perfectly cosmopolitan form which breeds commonly about houses in all parts of the civilized world and is, in temperate regions especially, the commonest inhabitant of rain water barrels. This species was long considered as perfectly typical of the genus not only in structure but in life-history; but the extended studies of other species have indicated remarkable differences in life-histories.

The eggs of *Culex pipiens* are laid in an irregular raft-shaped mass on the surface of the water. The mass is usually shaped like a pointed ellipse, somewhat convex below and concave above, all the eggs standing on end and closely applied side by side in from six to thirteen longitudinal rows, and from three or four to forty eggs in a row. The number in each batch varies from two hundred to four hundred. Individual eggs are

¹Since this article was put in type there has been great activity in the splitting up of the old genera and the erection of new genera of mosquitoes, and a condition of staple equilibrium has not yet been reached. To print a full synopsis of these late views would far exceed the limits of this work, and the writer therefore refers readers who wish to carry the subject of classification further, to Technical Bulletin No. 11, Bureau of Entomology, U. S. Department of Agriculture, entitled "A Classification of the Mosquitoes of North and Middle America," by D. W. Coquillett, Washington, 1906, page 31, 1 figure, which will be sent free to applicants.

.7 mm. long and .16 mm. in diameter at the base. The entire egg mass is about one-fourth of an inch in length. In summer weather the eggs hatch in from sixteen to twenty-four hours. The larvæ issue from the under-side of the egg mass and are very active at birth. They come frequently to the surface to breathe, and during the first few hours of their life may

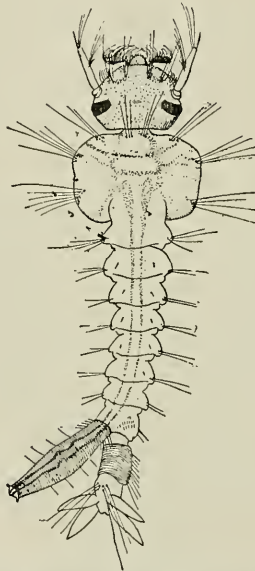
FIG. 13.



Culex pipiens: egg-mass and enlarged eggs. (Author's illustration.)

remain under the egg mass where they get air from the air film by which the mass is surrounded. The mouth of the larva, or "wiggler" as it is commonly termed, is furnished with tufts or filaments which are constantly in vibration. The head is large, the antennæ long, the thorax somewhat swollen, and the abdomen slender. The sides of the body are furnished with stiff bristles. There is a long breathing-tube which issues

FIG. 14.



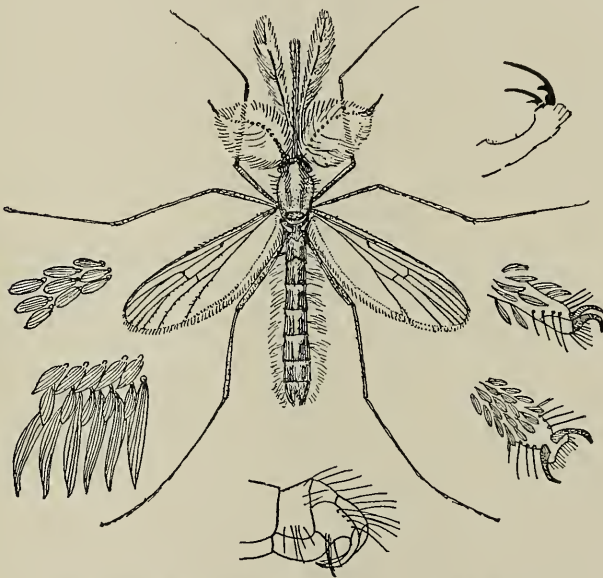
Culex pipiens: full-grown larva. (Author's illustration.)

from the next to the last segment of the abdomen, and this tube is thrust through the surface film of the water every time the larva rises to breathe. The extremity of the tube is furnished with a spiracle and into it run the two main tracheæ of the body. The true end of the body is furnished

with four flat flaps which in young larvæ probably function as air-gills. The specific gravity of the larva is somewhat greater than water, and it wriggles in ascending to the surface, but so slight is this difference in specific gravity that the tension of the surface film of the water is sufficient to maintain it without exertion while breathing.

In warm weather about seven days suffice for the growth of the larvæ and they then transform to pupæ. In this stage the insect breathes through two breathing tubes, one issuing from either side of the thorax. These are trumpet-shaped. The pupa is lighter than water and maintains its position at the surface without effort. It is active, and to escape its natural enemies may wriggle actively below the surface of the water. Immediately this exertion ceases, it rises rapidly to the top where it re-

FIG. 15.



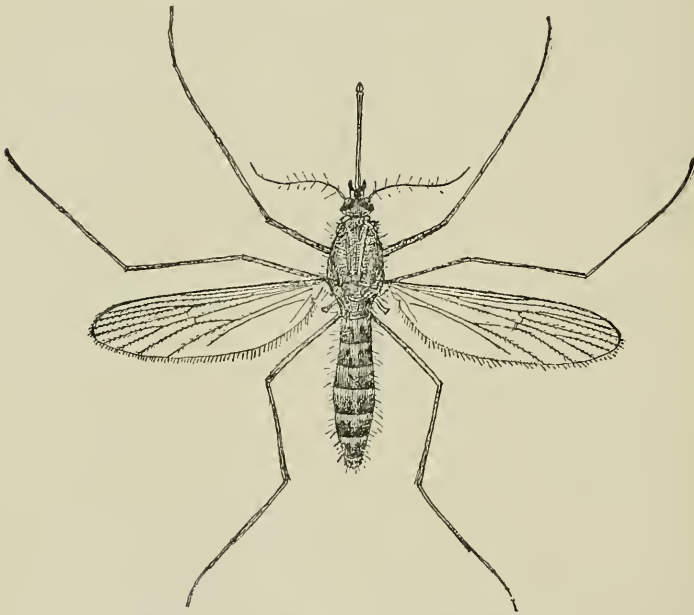
Culex pipiens: adult male and details. (Author's illustration.)

mains most of the time. In the pupal stage the insect remains, in mid-summer, about two days. A minimum generation of *Culex pipiens* will, therefore, occupy ten days—egg, sixteen to twenty-four hours, larva, seven days, and pupa, two days. In colder weather, however, the duration of this development may be indefinitely suspended. There is an indefinite number of generations each year, and the species will go on breeding so long as the temperature is favorable. The adult as a rule hibernates. In the neighborhood of two hundred species of the genus *Culex* have been described, and as before stated there is considerable variation in the habits and life-histories of the different forms.

The common salt-marsh mosquito of the Atlantic coast, *Culex sollicitans*, for example, according to the observations of Smith, does not lay its eggs in water or on the surface of water. The eggs must be dry, or not

water covered, for at least twenty-four hours after they are laid. Otherwise they will not hatch. They may remain dry for three months or longer without losing vitality, and if at any time, after they have been dry for a week or two, they become covered with water they hatch at once. It seems also from these observations that not all of the eggs hatch the first time they are covered with water, the others hatching upon the second covering. Eggs are laid in every damp space on the salt marsh and the country immediately adjoining it. They are not laid in raft-shaped masses, but singly. *Culex taniorhynchus*, also a salt marsh mosquito, lays its eggs as does *C. sollicitans*. *C. perturbans*, on the contrary, lays a raft-shaped mass, as does *C. pipiens*. *C. squamiger* has apparently but one generation each year, instead of many as with *C. pipiens*. *C. pipiens* bites

FIG. 16.

*Culex pipiens*: adult female. (Author's illustration.)

mainly at night, but *C. sollicitans* flies by day and bites when opportunity offers. The common woods mosquito, *C. sylvestris*, lays its eggs singly on the surface of the water, when they sink to the bottom, or they may be placed upon moist mud to hatch when the water comes. It appears to hibernate in the egg stage, although larvæ have been found in pools late in the autumn after ice has formed. A species commonly found in woodland pools, *C. canadensis*, as with several others, hibernates in the egg stage and is one of the earliest mosquitoes to bite in the spring. The flight of the species of *Culex* seems to vary considerably. *C. pipiens* is not a strong flier, and is in no sense a migratory mosquito. It stays about houses and flies no further than is necessary to secure food and lay its eggs. *C. sollicitans*, on the other hand, is said by Smith to fly for long distances inland

from the sea coast where it breeds. He finds swarms of this mosquito forty miles from the coast; and in none of his experiments has he been able to breed it from fresh water. It is perhaps worthy of note that what is apparently this species has been bred by Mrs. Hinds in Texas and by Dupree in Louisiana, from fresh water; but this is probably a case where we have adults which are specifically indistinguishable but which may really be specifically distinct. *C. territans*, a rather common small species, lays its eggs in rafts smaller than those of *C. pipiens*. The larva is very remarkable, having an enormously long, slender air-tube. The head is very broad with prominent antennæ which are black at the tip and have a tuft of long hairs near the end. It seems to prefer cold water rather than

FIG. 17.

*Culex sollicitans*: adult female. (Author's illustration.)

warm, stagnant pools. *C. triseriatus* lays its eggs singly or in patches at the edge just below the surface of the water where they adhere slightly and remain unhatched until spring. This species is probably single brooded. *C. dupreei* has a larva which seems to be truly aquatic and never comes to the surface of the water to breathe. The larva of *C. discolor* also apparently rises to the surface very seldom.

No such extraordinary variation among species seems to occur with other genera of Culicidæ, and the generalizations which may be made concerning the life-history of Anopheles are much more perfect.

MOSQUITOES OF THE GENUS ANOPHELES.

As indicated in the synoptic table, the principal structural difference between the adults of *Anopheles* and *Culex* is the presence of long palpi in the female of *Anopheles* and of very short palpi in the female of *Culex*. With *Anopheles* the palpi in both sexes are about as long as the proboscis. The body colors are brown and yellow, and the wings are usually spotted. Members of the genus *Anopheles* may rather easily be recognized when at rest, since the body, head, and beak are held in practically the same plane, whereas there is a marked angle between the body and the head and beak in most other mosquitoes. It is the habit of most species of *Anopheles*, in resting upon a horizontal wall like a ceiling, to hold the body not parallel with the wall but at a distinct angle with it—sometimes approximating 80°. Frequently with some species, even when on a perpendicular wall, this angle of rest is very obvious.

As a rule the *Anopheles* mosquitoes bite only after nightfall, but an exception must be made in the case of *Anopheles crucians* which will bite during the day. This is a matter of importance, since it has heretofore been believed that shelter from mosquitoes after nightfall obviates all danger from malaria. Even *Anopheles punctipennis* has been seen by Smith in the afternoon on porches, and Dyar has known it to bite by day. It has not been proven definitely that this species will carry malaria, and in fact its presence in large numbers in portions of New Jersey where malaria is unknown and yet where cases of malaria must frequently be brought, would indicate that in this species we have possibly an exception to the disease-bearing function of the genus.¹

The *Anopheles* mosquitoes do not seem to be strong fliers, and there are no instances on record known to the writer which prove a longer flight from breeding places than half a mile, which of course is an important point in the problem of the extermination of *Anopheles* by means of the abolition of breeding places or their treatment with insecticides.

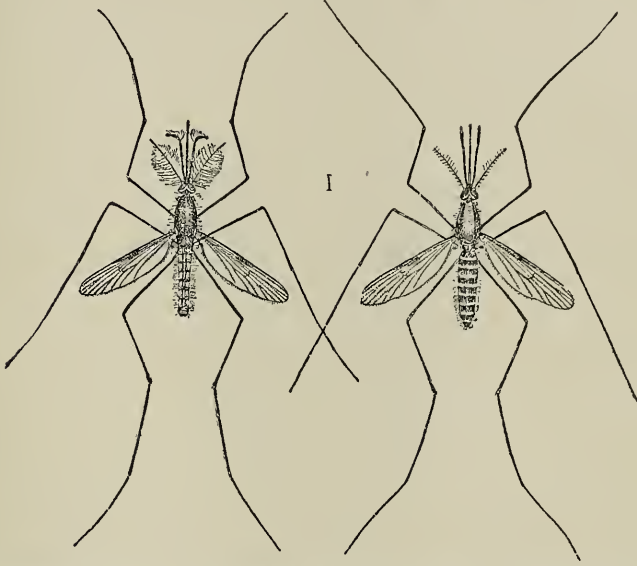
All the species of *Anopheles*, differing from many woodland and swamp mosquitoes, make every effort to enter houses. Hibernation is almost uniformly in the adult stage, and in regions where they breed abundantly, the cellars of houses, barns, and other outbuildings will be found to be favorite places of hibernation. They are often found thickly massed on the inner walls of outhouses, and have been seen during winter on the dark underside of shelves in cellar storerooms, so close together that their bodies touched, for a space of several feet. There are a few recorded instances of the hibernation of the European *Anopheles bifurcatus* in the larval condition, the most marked having been in Switzerland where the larvæ of this species were found in the vicinity of Lausanne hibernating beneath the ice in January, February and March.

The life-histories of all the species are very similar, and the differences among the early stages of the different forms are slight; so that the full life-history of a single species may in a measure be considered typical of the genus. *Anopheles maculipennis*, one of the commonest forms in the

¹Since this was written, Dr. J. W. Dupree of Baton Rouge, La., has sent the writer a paper in which he states that he has discovered the malarial relation for this species.

United States, has a wide distribution, occurring also in Canada and throughout Europe. It has not as yet been found in Asia or other parts of the world, and it is quite possible that it was introduced from Europe into the United States; in fact, it is possible that malaria itself was so introduced, although the recorded prevalence of fevers among the early settlers of Jamestown and other portions of this country would antagonize this theory.

FIG. 18.



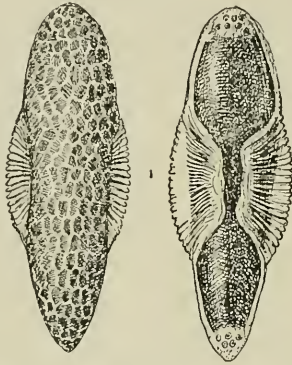
Anopheles maculipennis: adult male at left, female at right. (Author's illustration.)

The eggs of this species are laid singly upon the surface of the water, and are usually found in little groups. Each egg is boat-shaped and one end is slightly deeper and fuller than the other. When first deposited they are white, but soon darken. The upper surface is marked by minute reticulations, and the under surface by much larger and more regular reticulations dividing it into hexagonal areas. The rim is thickened and regularly ribbed. Along the centre of each side the rim is much thickened and the ribbing is more marked, the thickening recalling the rounded float which runs along the edge of a life-boat. It is composed of air-chambers and keeps the egg with its flat surface uppermost. Nuttall and Shipley have called attention to the fact that when the egg is drawn, by capillary attraction, a little way up from the water upon a leaf or blade of grass, the blunt end always points downward, so that when the hatching takes place the larva emerges into the water and not into the air. Each female deposits from forty to a hundred eggs. In warm weather they hatch in from three to four days, the young larva issuing from a circular split near the blunt end.

During the early part of its life the larva remains habitually at the surface of the water. Its breathing-tube is extremely short, and the body is

held parallel with the surface and immediately below the surface film, so that portions of the head as well as its breathing-tube are practically out of the water. The head rotates upon the neck so that the larva can turn it around with the utmost ease and feeds habitually with the under side of the head toward the surface of the water. This is its customary feeding position. The long fringes of the mouth parts are constantly in rapid motion, causing a constant current toward the mouth-opening so that all particles floating on the surface of the water gradually converge toward the mouth at an increasingly rapid rate and finally enter the alimentary canal. Spores of algae and minute particles of all kinds, organic and inorganic, floating upon the surface of the water follow this course and

FIG. 19.



Anopheles maculipennis: eggs, greatly enlarged. (Author's illustration.)

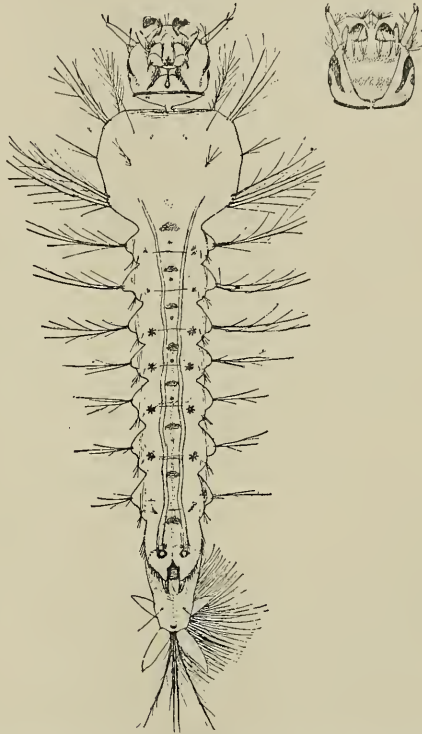
enter the mouth of the larva. Seen under the microscope, those objects which are dark in color may plainly be seen to pass through the head into the thorax. From the fact that it feeds upon these very light floating particles, the specific gravity of the body of the larva is nearly that of the water. It is much lighter than the larva of *Culex*, which feeds habitually upon particles held in suspension at a lower level, and the *Anopheles* larva maintains itself horizontally just below the surface film without apparent effort. The tension of the surface film itself seems to afford all needed support.

The structural characters of the larva are very distinct and at once separate it from the larva of any other genus of mosquitoes. The head is small; the respiratory tube is extremely short; the body is furnished with very long, lateral, branching hairs, and upon the upper surface of each of five of the abdominal segments there is a pair of specialized palmate hairs each with a stalk and a conical bundle of fine hairs, the whole forming a little cup; and it is thought that it is by means of these five pairs of palmate hairs, which cling to the surface film, that the larva maintains its horizontal position just under the surface. The ninth abdominal segment bears below a fan-shaped arrangement of long hairs. The larvæ in moving on the surface swim tail foremost. As they approach full-growth, they descend frequently to the bottom of shallow pools, and, where this is covered with sand, may be seen mouthing over the slimy surface of the

sand grains. The duration of the larval stage is, in midsummer, from sixteen to twenty days.

In the pupal condition *Anopheles* differs less markedly from other mosquitoes than in the larval stage. In its resting position at the surface of the water it is less perpendicular than the pupa of *Culex*, the long axis of the body being horizontal. There is a marked difference in the shape of the two thoracic respiratory tubes, those of *Anopheles* being short and with a much less slender base. The pupal stage lasts, in midsummer from three to ten days.

FIG. 20.



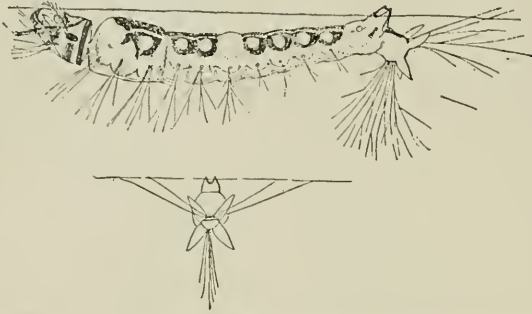
Anopheles maculipennis: full-grown larva, with head reversed, in feeding position.
(Author's illustration.)

The minimum duration of a generation in the summer time in the latitude of Washington is probably about twenty days or perhaps a little less. This period may be extended indefinitely by cooler weather.

The female *Anopheles* will bite a number of times, and in laboratory experimental work it is usually found necessary to give a female *Anopheles* a full meal of blood before she can be induced to deposit her eggs, although Dupree has induced fertile oviposition without the meal of blood. After the first breeding, no further sanguinary diet seems to be necessary and adults may be kept alive for some time by feeding them upon bananas or other fruit.

The genus is one of wide distribution, and this distribution corresponds fairly well with the distribution of malarial diseases, the range of *Anopheles* mosquitoes, however, being greater than the range of the disease since there are very many localities where *Anopheles* exist in numbers and

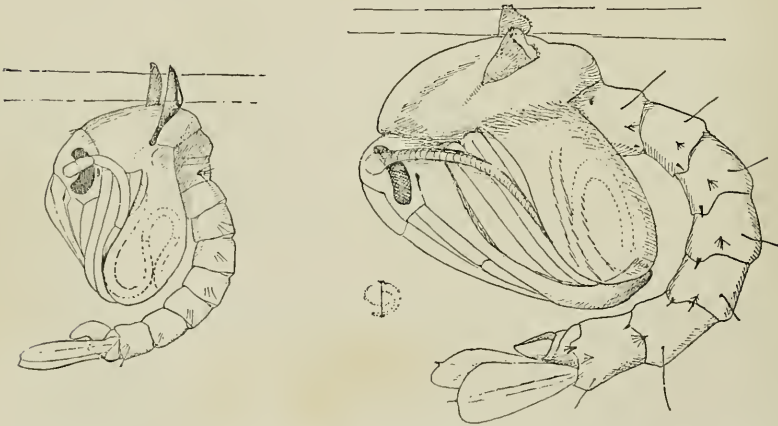
FIG. 21.



Anopheles larva at surface of water, showing resting and feeding position.
(Author's illustration.)

where malaria has not been introduced. Just as the disease itself is one of low altitudes, so the mosquitoes of this genus prevail in low-lying situations. They are seldom found in numbers above an altitude of one thousand feet, although in the tropics they are found at a considerably higher

FIG. 22.



Mosquito pupæ in resting positions at surface of water; *Culex* at left, *Anopheles* at right.
(Author's illustration.)

altitude. They have even been found in the City of Mexico at an altitude of nearly eight thousand feet, although they are comparatively scarce and malarial diseases are practically unknown, as the writer is informed by health authorities resident in that city. No species occurs in the far North, as is quite to be expected from their absence at considerable elevations.

In the number of species the genus is a very extensive one, although its distinct forms are not so numerous as the species of the genus *Culex*. In the United States there are seven recognized species, which may be distinguished by the following synoptic table:

GENUS ANOPHELES.

1. With a yellowish-white spot near three-fourths the length of the first margin of the wing..... 3
Without such a spot..... 2
2. Scales of the last vein and the palpi wholly black..... 5
Scales of the last vein white, marked with three black spots, palpi marked with white at bases of last four joints..... *crucians* Weid.
3. Hind feet wholly brown..... 4
Hind feet largely snow-white on the apical half; West Indies, Mexico, Central and South America:
Last joint of hind feet wholly white..... *argyritarsis* Desv.
Last joint black at base..... *albipes* Theob.
4. Scales of last vein white, those at each end black, scales of third vein black, those at the apex white..... *punctipennis* Say.
Scales of last vein white, those toward the apex black, scales of third vein white and with two patches of black ones.. *franciscanus* McCrack.
5. Wings with several dark spots..... *maculipennis* Meig.
Wings unspotted..... *barberi* Coq.

Several other species have been attributed to the United States. Of these, *Anopheles ferruginosus* of Wiedemann is probably a synonym of *crucians*; *quadrimaculatus* of Say is a synonym of *maculipennis* of Meigen; and *hiemalis* of Fitch is a synonym of *punctipennis* of Say. *A. nigripes* Staeger, a European species with unspotted wings, is said to occur in northern Europe and North America, but the locality and collector are unknown to the writer. *A. pictus* of Loew was described from Asia Mi-

FIG. 23.

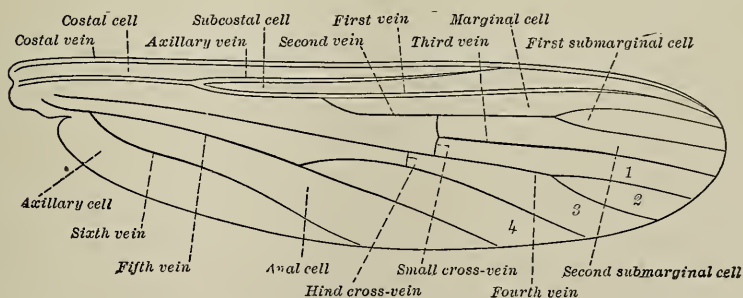


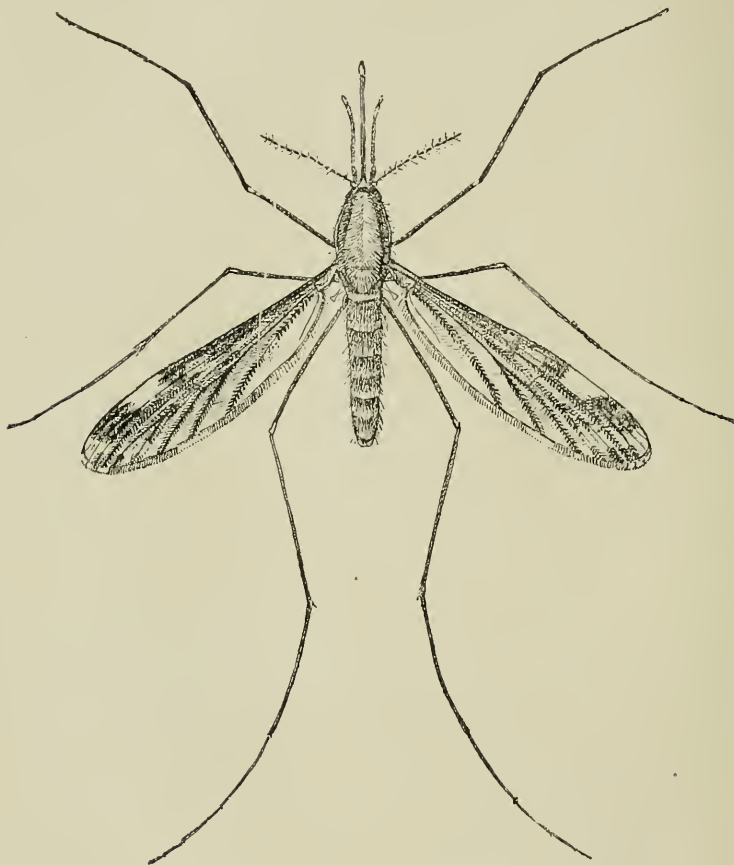
Diagram of mosquito wing, with names of veins and cells. (After Coquillett.)

nor, and its occurrence in the North American fauna is very doubtful. *A. walkeri* of Theobald also has unspotted wings, and is said by Theobald to have been captured at Lake Simcoe, Ontario, in September. It is now supposed to be a synonym of the European *A. bifurcatus*.

Probably the commonest and the most widely distributed of these species is *Anopheles maculipennis*. It is not a striking looking form, being

of medium size and of general insignificant coloring. The wings have a slight yellowish cast, and bear four rather small dark spots. As pointed out in the synoptic table, the scales of the last wing-vein and the palpi are entirely black. Its European distribution has already been referred to, and in the United States it is widespread. It occurs abundantly about New York City and on Long Island. Felt records it as occurring about Albany, and through the central part of New York State it is a compara-

FIG. 24.

*Anopheles punctipennis*: adult female.

tively common species. In New Jersey, Smith finds that it occurs throughout the state, and, although in general it is less numerous than *A. punctipennis*, it is on the whole more plentiful in the northern and hilly sections of the state. It is found about Boston and in other parts of New England. It occurs in all of the Atlantic States to Florida, in all of the Gulf States, in Ohio, Wisconsin, Minnesota, Idaho, California, and south into Mexico. It also occurs in Canada.

Anopheles punctipennis is a much more distinctive looking species. The general effect of the wings is that they are greatly mottled, and there is a characteristic and distinctive yellowish-white marginal spot near the apical fourth of the wings. It is of medium size and of dark brown color, and the beak and legs are unbanded. It is very widely distributed throughout the United States, and occurs also in Canada, but its distribution is northern rather than southern. It is found in the New England States, New York, the Atlantic Coast States certainly as far north as North Carolina and Louisiana, the Central States including Minnesota. It has been found as far north as St. John, New Brunswick, and as far southwest as Salvatierra, Mexico. It also occurs in California.

FIG. 25.

*Anopheles crucians*: adult female.

Anopheles crucians, as compared with the preceding species, has rather a southern than a northern distribution. It is at once distinguished from the other species by the white bases of the last four segments of the palpi, and by the white scales on the last wing-vein, which, however, is marked with three black spots, while the disk of the wing carries several black patches. As pointed out by Smith, this species flies and bites freely long

before dusk and long after sunrise. He finds it to be the most annoying indoor form at Cape May and that its chief breeding place in New Jersey is in the Cape marsh. The species also occurs rather abundantly on the south shore of Long Island. It extends down the Atlantic coast to Miami, Florida, and is also found in Cuba. It occurs in the Southern States west to Texas.

Anopheles albipes is distinctly a tropical and subtropical form. It occurs throughout the West Indies and at various points in Central America as far south as Panama. It has been taken at Key West, Florida, and is reported to occur in India. It is a striking mosquito in general appearance, and is distinguished by its silvery-white hind tarsi, the last joint only being black at the base.

Anopheles franciscanus is sufficiently characterized in the synoptic table, and is a western form occurring at various points in California. It has also been found at Laredo, Texas, and at Las Vegas, New Mexico.

The American *Anopheles* with unspotted wings, *A. barberi*, is a rare species, and breeds in hollow trees in the woods. It was originally found at Plummers Island, Maryland, and has since been taken in Virginia and at St. Louis.

Anopheles argyritarsis is a form of tropical and subtropical distribution, as is *A. albipes* from which it may at once be distinguished by the absence of the black mark at the base of the last tarsal joint. It has practically the same distribution as *A. albipes*. It has been taken at New Orleans and may breed there, although the constant traffic between that port and Central America and West Indian points renders the introduction of the species very easy and its capture does not necessarily mean that it is established in Louisiana.

Anopheles albipes and *Anopheles argyritarsis* have been placed by Theobald in his genus *Cellia*, which is distinguished from *Anopheles* by the dense scaling of the wings, and by the presence of nearly erect clusters of scales along the sides of the abdomen. The habits and larval characteristics are, however, those of *Anopheles*, and there is little doubt, since they are the prevalent species of the *Anopheles* group in malarial localities in the West Indies and Central America, that they are malaria carriers. In fact this relation has been proven in the case of *argyritarsis* by Lutz, and in the other by Low.

THE GENUS STEGOMYIA.

The genus *Stegomyia* was separated by Theobald from *Culex*, by the fact that the scales of the head and scutellum are all flat and broad, whereas in *Culex* the scales of the head are narrow and curved with upright forked ones and flat lateral ones. Sixteen species were originally placed by him under this genus and eight were later described and transferred to this genus, but certain of these have since been placed in other new genera. The genus itself may not prove to be a stable one. Surely the differing life-histories of some of the forms would indicate further separations. No generalization can be made regarding the disease-bearing possibilities of the genus, since only a single species, *Stegomyia calopus*, has been shown to carry a disease—yellow fever.

Stegomyia calopus has a wide distribution. In general terms Theobald considered it as ranging from 38° south to 38° north latitude, the belt extending around the world. It seems to have a general distribution throughout all eastern Australia, western Sumatra, all of Java and farther India, southern Japan, eastern Hindostan, the Seychelles, southern Africa, Mashonaland, Nigeria, the African west coast including Senegambia and Lagos, all of Spain, southern Italy, Palestine, east coast of South America from British Guiana to Rio de la Plata, all of the West Indies, Argentina, the coast regions of Central America on both the Pacific and Gulf of Mexico sides. It is also found at Guayaquil and Callao and will undoubtedly be found at other South American ports in the western coast as far south as Valparaiso. It is also found in the Fiji Islands, the Hawaiian Islands and the Philippine Islands.

The Central American distribution of the species is of especial interest as bearing upon the possibilities of its occurrence at high elevations. It is stated above that it occurs upon both the east and west coasts of Central America. In Mexico, since the introduction of railroads running up from the coast, it has been extending its inland and upward range. It has now established itself at Orizaba on the Vera Cruz road at an elevation of 4,200 feet, and at Carasal on the Inter-oceanic Railroad at an elevation of 3,000 feet. It occurs abundantly inland in North Mexico, having followed up the valley of the Rio Grande, and occurs at all points on the railroad from Tampico to Monterey (altitude 1,630 feet). It has been found in the summer time at Saltillo, which is much higher than Monterey.

In the United States it occurs and breeds continuously in practically all of the territory which has been marked as belonging to the Lower Austral Life Zone. This territory includes the Atlantic coastal plain from the mouth of the Potomac River southward, and all of the Gulf States except the high regions of Georgia and Alabama about the southern end of the Appalachian chain. It also includes the valley of the Mississippi River for some little distance above its juncture with the Ohio River, the valley of the Ohio River to nearly the middle of the southern border of Indiana, the whole of Indian Territory, the eastern portion of Oklahoma, a small southeastern strip in Kansas, and all of the low-lying eastern and southern portions of Arkansas. The dry regions of western Texas do not furnish sufficient moisture to propagate many mosquitoes, but in the water supply of ranches in such dry regions, if once introduced, the yellow fever mosquito will probably breed. Although found on the Pacific coast of Mexico, the yellow fever mosquito has not as yet been authoritatively recorded from California, although the coastal region from Point Vincent south to Point Loma offers conditions favorable for its development. Actual collections of mosquitoes were made during the season of 1904 through a large part of this Lower Austral territory, and the distribution of *Stegomyia calopus* was found to correspond rather exactly with the lines here laid down.

The northward spread of this species is interrupted by severe winters. In summer time it is constantly being carried north on boats up the Mississippi and Ohio Rivers and by trains coming from the South. Thus it has been found breeding, in the summer time, at points considerably north of true Lower Austral territory. During the summer of 1904 it was found breeding at St. Louis but the severe winter weather precludes the possibility of the perfect establishment of the species at that point.

Stegomyia calopus is a rather small mosquito, which was formerly referred to in literature as *Culex fasciatus* and as *Culex taniatus*. Purists are now calling it *Stegomyia calopus* Meigen, since *fasciata* seems to be a homonym. It is a very handsome species, dark in color, with silvery white bands on the legs, conspicuous silvery stripes upon its thorax, silvery bands on the palpi, and silvery spots on the sides of the thorax and abdomen. In the British West Indies it is known as the striped-legged mosquito and also as the day mosquito. It bites and is active by day, but may also bite at night. It breeds only in fresh water and is essentially a domestic mosquito—that is to say, it is seldom found far from human habitations; but about houses and in cities and towns it will breed in any chance accumulation of water. It is a long-lived mosquito, a point of importance when considering the interval between the stamping out of an epidemic and a new outbreak without the introduction of a new case from a distance. Guiteras and his assistants at Las Animas Hospital have kept an adult female alive for more than 150 days; and in the dry season with no opportunity to oviposit such a length of life is probably of frequent occurrence. The length of flight has not definitely been determined. It does not seem to be an especially strong flier, but its possibilities in this direction are of importance as determining the safe anchorage distance of vessels from infected ports. Adult mosquitoes have been found on board a war vessel recently arrived in port and anchored a mile from shore, under conditions that seem to show that the mosquitoes flew aboard, the vessel previously having been free, and the possibility of the carriage of the mosquitoes from shore on the persons of individuals in boats having apparently been eliminated. This is on the evidence (in *lit.*) of Surgeon A. H. Russel, U. S. N.

The eggs are deposited singly, each egg on its side, and preferably in artificial collections of water, especially in rain-water barrels and similar receptacles. The eggs may be found singly or in groups of three or more arranged in parallel rows or bunched together. They are black in color, cylindrical in shape, with conical extremities, of which one is blunter than the other. Each egg is .6 mm. long and .16 mm. broad. The female may deposit from 35 to 114 eggs at a time, the average being about fifty. These eggs will withstand desiccation, and are very resistant to external influences. Taylor has kept thoroughly dry eggs for three months, which hatched on being placed in water. Normally the eggs will hatch in from twelve hours to three days, depending upon the temperature of the water.

The larva is similar to that of *Culex pipiens*, but it is more slender and the respiratory tube is shorter and is swollen in the middle somewhat resembling an olive in shape. The growth of the larva is very rapid, and in Cuba the minimum seems to be about six days. The larvæ develop most rapidly in foul, stagnant water, and the development may be hastened by placing a certain amount of fecal matter in the water.

The pupa is rather dark in color, with more elongate thorax and a stouter abdomen than *Culex pipiens*. The minimum duration of the pupal stage is two days, and the minimum length of the early stages is therefore eight and a half days (egg twelve hours, larvæ six days, pupa two days).

REMEDIES AGAINST MOSQUITOES.

The very best remedy against mosquitoes is to abolish their breeding places, and in many instances this may readily be done with isolated country houses or suburban residences or in villages where the houses are as a rule well separated and surrounded by gardens. In such localities, barring the vicinity of extensive swamp lands, and outside the range of flight of the salt marsh mosquito, every property holder is practically responsible for his own mosquitoes. Every effort should be made to clear out or to abolish chance breeding places. Disused springs and wells should be cared for, and every possible receptacle for standing water should be abolished or filled in. Cesspools should be covered in such a way as to render mosquito access impossible or they should be treated occasionally with kerosene. About a country place or suburban house chance breeding places are apt to be very numerous. Tin cans and old bottles in a rainy summer will hold sufficient water to breed hundreds of mosquitoes. The water pans for pet animals or for chickens are also breeding places, as are the water troughs for horses. The roof gutters of the house where trees overhang are apt to be clogged to some slight extent and thus afford enough resting water to breed generations. Rain water barrels and tanks should be carefully screened. All depressions in the soil in which surface water may rest for even so short a period as a week in midsummer should be filled in. The banks of any little brooks or rivulets should be kept clean so as to allow no opportunity for standing water or any amount of aquatic vegetation. Ponds which cannot be drained should be treated with light fuel-oil, preferably by spraying. Where for one reason or another it is considered impracticable to use oil, such ponds should be stocked with fish. Gold-fish, silver-fish, sun-fish, top minnows, killifish, and various other minnows are capital mosquito destroyers.

In localities near salt marshes or fresh water swamps, the difficulty is much greater. Even in such places, however, strictly local work will greatly reduce the mosquito supply, and large-scale work is by no means impracticable. The recent work of the State of New Jersey, as reported by its State Entomologist, Dr. John B. Smith, has shown that the difficulty of draining salt marshes is not very great, and that the filling in of large areas is perfectly practicable. Inland the drainage of most swamps is practicable. For example, very perfect results in swamp drainage are shown in the reclamation of the Potomac marshes near Washington.

In many communities the work of mosquito extermination has been undertaken by organizations of public-spirited citizens, but with proper legislation and with the proper public spirit this should not be necessary. The health-law of every state should contain a clause which places waters or pools, in which mosquitoes breed, among the nuisances that may be abated by local boards of health, and they, after due notice to the owners of the places, should be empowered, in case the owners fail to do so, to undertake the work and to abate the nuisance, the cost being charged to the owners of the property. Such legislation is in effect in New Jersey and should be in other states.

THE COLLECTION AND BREEDING OF MOSQUITOES.

Adult mosquitoes may be captured in a small, soft net or more easily by placing over them when at rest a small inverted vial. They are readily stifled by tobacco smoke or by a drop of chloroform, or may be killed in the ordinary cyanide collecting-bottle used by entomologists. A good collecting-bottle may be made by soaking a few rubber bands in chloroform and placing them in the bottom of a vial with a layer of blotting paper over them. They will give off enough chloroform fumes for a month or more to kill mosquitoes and other delicate insects.

For permanent preservation, mosquitoes may be gummed with white shellac to the tips of small cardboard triangles, and the triangles pinned with an insect pin through the base.

In rearing mosquitoes the rearings should be isolated, except perhaps when they are made from eggs deposited at one time by a single determined female. Even here it is well to isolate the larvæ, since with certain species they destroy each other. Where larvæ are collected in a pool, isolation is necessary since several species may inhabit the same pool at the same time. A single larva should be reared in a single receptacle. When the larva pupates, the cast larval skin should be saved in a small bottle of formalin or alcohol or on a slide. When the adult emerges the pupal skin should be added, and the adult and skins should be numbered with the same number.

Since one usually has an insufficient number of jars to isolate all or a large proportion of the larvæ in each culture, it is well first to put them in a shallow dish and isolate those that appear to be different. The rest should be left in a general culture and watched closely for the appearance of forms not noticed at first. Breed all of the larvæ to adults, unless reasonably sure that the culture is composed entirely of one species, in which case the remaining larvæ can be preserved in formalin or alcohol. Mosquito larvæ need food, and if they are small the water must be renewed, by preference from the original source with some of the bottom matter. Too much fresh matter will often kill the larvæ, possibly by the over-development of bacteria. Isolated pupæ should be put into clean water with no organic matter. The larvæ should not be crowded after collection, and enough air space should be left at the top of the jar or vial to insert a cork if necessary.

Anopheles larvæ, being surface-feeders, need a broad, shallow pan, uncovered and preferably placed in a bright light. They cannot be bred successfully in small, deep vessels unless full-grown and nearly ready to pupate.

These recommendations are based upon Dr. H. G. Dyar's extended experience in breeding mosquitoes, and in the study of their early stages.

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CHAPTER XIX.

THE MALARIAL FEVERS.

By CHARLES F. CRAIG, M.D.

Synonyms.—Wechselfieber; intermittent and remittent fever; tertian, quartan, or æstivo-autumnal fever; paludal; climatic fever; swamp or marsh fevers; ague; paludal fever; hill fever; jungle fever; mountain fever (in some localities); coast fever; gnat fever; hæmamœbiasis; cameroon fever; febbre intermittente; paludisme; maladies palustres; fièvre paludéenne.

Definition.—By the term malarial fevers we mean a group of specific infectious fevers due to infection of the red blood corpuscles of man by closely related animal parasites belonging to the *Sporozoa*, genus *Plasmodium*.¹

These fevers occur epidemically or endemically and are accompanied by a symptom complex which is more or less characteristic of each variety. Periodicity is one of the most marked clinical phenomena and is due to the growth and multiplication of the plasmodia. Clinically, these fevers may be divided into intermittent, remittent and continuous, but such a classification is unscientific as it does not indicate disease entities. All malarial infections are transmitted by mosquitoes of the genus *Anopheles*, and so far as is known at the present time, this is the only means of transmission.

Historical.—It is very probable that the ancient Egyptians had some knowledge of what we now term the “malarial fevers,” and Groff considers that certain inscriptions upon the temple at Denderah are proof of this assumption. Hippocrates and Celsus described very accurately the manifestations of the various forms. Hippocrates (406–377 B. C.) divided them into quotidian and tertian, and Celsus (first century, A. D.) further distinguished the pernicious forms.

Morton² was the first to associate these fevers with miasmatic conditions, clearly indicating his belief that they were due to noxious gases arising from low lands and swampy districts.

¹The malarial parasites belong to the *Sporozoa*, sub-order *Hæmosporidia*, genus *Plasmodium*. The name *Plasmodium* was first given to these organisms by Marchiafava and Celli, and is very unfortunate from a biological standpoint. Grassi has suggested the name *Hæmamabæ* for the parasites, and this is a preferable term to *Plasmodium*, but the latter term will have to be retained because of the law of priority. The same objection may be raised to the name “malaria,” which was derived from the Italian, meaning bad air, and applied to these fevers because of the supposed relation of miasmatic conditions to their causation. In the light of our present knowledge the name is erroneous, but will have to be retained as it has become so firmly established in our nomenclature.

²*Pyretologia*, London, 1692.

The introduction of cinchona into Europe by the Viceroy Del Cinchon in 1640 gave an impetus to the study of malaria, as it thus became possible to distinguish malarial fevers from other infections by the therapeutic test. The term "malarial" was not applied to these fevers until 1712, when Torti¹ published a classical description of the pernicious malarial infections and distinguished them by their yielding to cinchona. Meckel, in 1847, and Virchow, in 1848, first described the melanæmia which is invariably present in these infections, and it is probable that they actually saw, without recognizing them, the malarial parasites.

It was not until 1880, however, that the etiological factor in the production of malaria was discovered. Laveran,² a French Army Surgeon, stationed at Algeria, after careful study of the blood of many cases of malarial fever, announced the discovery of a parasite in the blood which he had no hesitation in claiming to be the veritable cause of the disease. At first his researches attracted little attention but they were soon confirmed by many observers, and his claim to have discovered the actual cause of malaria abundantly verified.

Although by Laveran's great discovery the diagnosis of malaria was placed upon a scientific basis, but little was known regarding the means of transmission of the parasites, and it remained for Ross, in 1897, to clearly demonstrate that the hæmatozoa of birds were transmitted by a certain species of mosquito. Grassi and other investigators soon confirmed the investigations of Ross, and proved that all varieties of the malarial fevers are transmitted from man to man by mosquitoes of the genus *Anopheles*.

Geographical Distribution.—There is no infectious disease which can compare with the malarial fevers in the extent of its geographical distribution. In the Eastern hemisphere malarial infections do not occur above 62° N. Latitude, while in the Western hemisphere they are very rarely found above 45° N. Latitude. They are most common and severe in low-lying coast regions, mountainous countries being comparatively exempt. The deltas of large rivers, especially the rivers of tropical countries, are hot-beds of malarial disease, and this is also true of all bodies of water situated in such localities. As the equator is approached we meet less often with the benign forms of malarial infection, the prevailing types being the severe and often fatal æstivo-autumnal infections.

The most important malarial localities are the following:

North America.—In North America, malaria occurs rarely above the forty-fifth parallel, but is often frequent and fatal in the Southern states and in the West Indies, especially in Cuba, as well as in Central America. In the New England and Middle Atlantic states the benign forms are present, but are comparatively rare. The severe forms prevail along the low regions of the southern coast line, and especially in the swampy regions of the Gulf states. These infections are common and severe along the Mississippi River and its southern branches, and they are present in many of the Western states, especially in the river valleys of California where severe and fatal æstivo-autumnal infections are not uncommon. The regions about the Great Lakes are almost free from malaria except in certain localities about Lake Michigan. Canada is the only country in North America which appears to be almost entirely free from malaria.

¹ *Therapeutica specialis ad febres quasdam perniciosas.*

² *Bulletin de l'Académie de Médecine de Paris*, séance de 23, Nov., 1880.

South America—In South America, severe types of the disease are common, especially along the coast regions of Colombia, Venezuela, Guiana, Brazil, Ecuador, Peru and Chile. The whole Atlantic coast line of Central America is severely infected with æstivo-autumnal malaria, and in this region the most pernicious forms are common.

Europe.—Malarial fevers occur but rarely in England, Germany and France. In Germany they occur along the coast of the Baltic, especially in Prussia, and they are not uncommon in the swamps of Hanover and Westphalia, and along the Rhine; in France these infections occur along the Loire and Rhone on the west coast; in Spain the valleys of the Tago and Guadalquivir are infected, and pernicious forms occur in all the countries bordering upon the Mediterranean; in Greece, Crete, Italy, Sicily, and Turkey, malaria is endemic; in Italy, especially, occur the most malignant forms in the regions around the Roman Campagna and the Pontine marshes, as well as in the valley of the Po; in Russia malarial infections are present in the valley of the Volga, Dniester, and Dnieper, and they are also common in the regions bordering upon the Black and Caspian Seas.

Asia.—India, Ceylon, portions of China and Arabia, and the Islands of the Malay Archipelago are infected with the malarial fevers. This is also true of Asia Minor and the valleys of almost all the great rivers, such as the Indus and Ganges. In Japan the benign infections are common, and even upon the lofty table lands near the Himalayas malarial infections are often met with. The Philippine Islands, until very recently considered as comparatively free from malarial disease, have been proved to be badly infected, a large percentage of our soldiers returning from there showing infection with the tertian and æstivo-autumnal parasites.

Africa.—In Africa are some of the most dangerous lurking places of malarial infections, the worst areas being those along the west coast and the Senegal, Congo, and Niger Rivers, as well as the regions around the great lakes and the jungles and lake shores of Abyssinia. Madagascar, Reunion, and Mauritius Islands present the pernicious varieties of the disease. Around Delagoa Bay and along the east coast of Africa, æstivo-autumnal fever is prevalent. Lower Egypt, the Soudan, the Nile delta, Tripoli, Tunis and Algeria, all harbor these infections.

The *resume* given indicates the most important localities in which malarial infections are endemic, but there are numerous districts in which a few sporadic cases occur at rare intervals, but which may at any time become endemic foci, provided certain species of mosquitoes belonging to the genus *Anopheles* are present, together with individuals harboring the parasites. A knowledge of the geographical distribution of malarial infections is, therefore, most important, as localities which are known to be infected can thus be avoided, and those who are residents of such localities can take the proper precautions to avoid infection.

THE MALARIAL PARASITES.

Etiology—The history of the discovery of the parasites concerned in the etiology of the malarial fevers furnishes one of the most interesting chapters in the annals of medicine. The theory that these fevers

might be due to parasitic infection is very ancient, dating as far back as 118 B. C., but little, however, was known concerning this subject until 1849, when J. K. Mitchell¹ suggested that certain spores occurring in marshy districts might be the etiological factor. In 1866, Salisbury² described certain small vegetable cells which he claimed to have found in the perspiration and urine of patients suffering from malaria, and which he considered to be the cause, and for a time his views were widely accepted. In 1879, Klebs and Tommasi Crudeli³ found in the soil of malarial districts, certain rod-shaped bacteria which, when injected into animals in pure culture, were claimed by them to produce the symptoms of the disease. Their observations were never confirmed by careful observers but for some time their views were accepted by a large proportion of the scientific world.

The bacterial origin of the malarial infections was believed in for a considerable period of time, although in 1880 Laveran⁴ described certain parasites occurring in the blood which he considered as the cause of the disease. His observations were soon confirmed by Richard, Marchiafava and Celli, Golgi, Councilman, Abbot, Sternberg, Osler and Dock. In his original communication Laveran described three forms of the parasite. The first consisted of oval or crescentic bodies with hyaline protoplasm containing pigment, arranged either in clumps or in a wreath-like arrangement. This form was undoubtedly the crescentic form of the parasite causing æstivo-autumnal malaria. The second form described consisted of small hyaline bodies containing pigment; and from these bodies there arose occasionally long, thin, hyaline filaments which possessed the property of motion. This form was undoubtedly the flagellated form of the æstivo-autumnal parasite. The third form described by him consisted of spherical, slightly granular bodies, with motionless pigment, which were evidently degenerative forms of the two foregoing classes. Richard⁵ later described the intracorpuseular hyaline parasites and the segmenting bodies. In 1885, Marchiafava and Celli⁶ described carefully the hyaline and intercorpuseular parasites, and proposed the term *Plasmodium malariae* for the organism. Biologically, this term is very inaccurate and should be abandoned, as the parasites belong to the sporozoa, but the name is so firmly fixed in our nomenclature that it will probably have to be retained. In the same year, Golgi⁷ proved that quartan fever depended upon a specific form of the malarial parasite, and shortly afterward he also differentiated and described the parasite causing tertian fever. To him we also owe the discovery that the malarial paroxysm always coincides with the segmentation or sporulation of a group of parasites. Occurring every forty-eight hours, this segmentation produces tertian fever, while if it occurs every seventy-two hours quartan fever is the type present. In 1885, Golgi also called attention to the probably distinct type of the crescentic and ovoid forms of the organism, and Councilman

¹On the Cryptogamous Origin of Malarious and Epidemic Fevers, Philadelphia, 1849.

²American Journal of the Medical Sciences, January, 1866.

³Arch. f. exp. Path. u. Pharmak., 1879, XI, 311.

⁴Loc. cit.

⁵Gaz. Med. de Par., 1882, 252.

⁶Fortschritte der Med., 1885, III, No. 24, 787.

⁷Arch. per le scienz. Med., X, 1886, 109-135.

first called attention to the diagnostic value of the various forms which are observed in the blood. In 1889, Golgi further added to his studies concerning the development of the crescents, showing that they arose from the small, cellular rings, and that this parasite was associated with fevers of remittent character. To him belongs the credit, therefore, of first clearly differentiating the æstivo-autumnal parasite. In the same year, Marchiafava and Celli added to Golgi's observations and gave a most accurate description of the æstivo-autumnal plasmodium.

Classification.—The classification of the parasites causing malaria has occupied the attention of zoölogists for many years, and a great many different opinions have been advanced regarding their exact position. At the present time it is conceded by all that they belong to the *Sporozoa*, and the classification of Schaudinn, adopted at present by nearly all authorities, is the one which will be followed in this contribution. He places the organisms under the sub-order *Hæmosporidia*, and gives three varieties, as follows: *Plasmodium vivax* (tertian parasite), *Plasmodium malariae* (quartan parasite), and *Plasmodium immaculatum*¹ (æstivo-autumnal parasite). The Italian authorities, together with nearly every investigator who has studied malaria in the tropics, have made a subdivision of the æstivo-autumnal parasite into two varieties, the quotidian and tertian. A large amount of labor has been expended in differentiating these varieties of the æstivo-autumnal parasite, and it is undoubtedly true that they can be differentiated when the material is available for study. From personal experience, the writer is satisfied that the quotidian and tertian æstivo-autumnal parasites can be as easily differentiated as the tertian and quartan.

The malarial plasmodia are found in man within the red blood corpuscles and are essentially parasites living upon and within these cells. In this situation they destroy the red corpuscles and produce the well-known anæmia peculiar to malarial fever, together with the pigmentation, or melanæmia which is due to the destruction of the hæmoglobin of the red cell. In describing these parasites in the light of our present knowledge, two life-cycles must be considered: first, the human cycle, schizogony or asexual cycle, occurring within the infected individual, and second, the mosquito cycle, sporogony, or sexual cycle, occurring within the infected mosquito. As has been stated, the only known method of transmission of malarial fevers is by the aid of certain mosquitoes belonging to the genus *Anopheles*. These fevers are not infectious from patient to patient except through the intermediation of certain mosquitoes.

Plasmodium Vivax—(The Tertian Parasite)—(Schizogony, Human Cycle).—The tertian parasite, or *Plasmodium vivax*, appears first within the red cell in schizogony as a small actively amœboid hyaline body, the *schizont*, of various shapes, the difference in outline being due to the rapidity and extent of the amœboid movement. At first the outline of the organism is very indistinct and careful examination is needed to distinguish it. As the organism grows older and becomes pigmented it is much more easily distinguished. The hyaline stage is quickly followed

¹ The name "*P. immaculatum*" is not correct. Blanchard has shown that Grassi previously used the terms "*immaculatum*" and "*præcox*" for parasites occurring in birds, which prevents their use for the human parasite. This makes Welch's term, "*falciparum*," the proper one.—Editor.

PLATE I

Fig. 1.—Tertian Malarial Plasmodium.

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| 1. Hyaline form. | 7. Segmenting forms. | 9. Non-flagellate form. (Macrogamete.) |
| 2. Pigmented ring form. | 8. Flagellate form. (Microgametocyte.) | 10. Segmenting form after destruction of red corpuscle. |
| 3 to 6. Pigmented forms. | | |

Fig. 2.—Quartan Malarial Plasmodium.

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| 1. Hyaline forms. | 8. Segmenting forms after the destruction of red corpuscle. | 9. Flagellate form. (Microgamete.) |
| 2 to 5. Pigmented forms. | | 10. Non-flagellate form. (Macrogamete.) |
| 6 and 7. Segmenting forms. | | |

Fig. 3.—Tertian *Æstivo-autumnal* Malarial Plasmodium.

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| 1 and 4. Hyaline ring form. | 8. Young intracorpuseular crescent. | 10. Flagellate form. (Microgametocyte.) |
| 2, 3 and 7. Pigmented ring form. | 9. Segmenting forms. | 11 to 14. Crescentic forms. |
| 5 and 6. Pigmented forms. | | |

Fig. 4.—Quotidian *Æstivo-autumnal* Malarial Plasmodium.

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| 1 to 4. Hyaline ring forms. Some cells show infection with more than one organism. | 8. Segmenting forms. Segmentation complete within infected red blood corpuscle. | 10, 11, 13 and 15. Crescentic forms. |
| 5 to 7. Pigmented forms. In 6 one hyaline form. | 9. Flagellate form. (Microgametocyte.) | 12. Ovoid form. |
| | | 14. Non-flagellate forms. (Macrogamete.) |

NOTE.—Mark the larger size and greater amount of pigment in the tertian *æstivo-autumnal* plasmodium.

PLATE II.

Fig. 1.—Tertian Malarial Plasmodium. Stained by Oliver's Modification of Wright's Stain.

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| 1 to 4. Ring forms of tertian parasite. | 11 to 14. Nearly full-grown forms, showing diffusion of the chromatin. | 18. Segmenting forms after destruction of red corpuscle. |
| 5. Ring form. (Conjugation form of Ewing.) | 15 to 17. Segmenting forms within red corpuscle. | 19. Flagellum. (Microgamete.) |
| 6 to 10. Pigmented organisms. | | 20. Sporozoite. |

Fig. 2.—Quartan Malarial Plasmodium. Stained by Oliver's Modification of Wright's Stain.

- | | | |
|---|---|--|
| 1 to 4. Ring forms of quartan parasite. | 10 to 12. Segmenting forms of quartan parasite. | 13. Segmenting stage after destruction of red corpuscle. |
| 5, 6, 7, 8, 9. Pigmented parasites. | | |

NOTE.—Chromatin of nucleus stained red; protoplasm stained blue; vesicular portion of nucleus unstained.

PLATE III.

Æstivo-autumnal Malarial Plasmodia. (Tertian.) Oliver's Modification of Wright's Stain.

- | | | |
|---|--|--|
| 1, 3, 4, 5, 6, 7, 8, 9, 10 and 15. Ring forms of tertian <i>æstivo-autumnal</i> plasmodium. | 12. Red corpuscle showing infection with two "ring forms." | 25 to 36. Crescentic forms of <i>æstivo-autumnal</i> plasmodium (tertian). |
| 2. Intracellular form. | 13 and 19. Pigmented forms, just prior to segmentation. | 29. Ovoid form. |
| 11, 13, 14, 16 and 17. Pigmented ring forms. | 20, 21, 23 and 24. Round and ovoid forms developed from crescents. | 37. Segmenting form. |
| | 22. Macrogamete. | 33. Sporozoites. |
| | | a. Segmenting form of quotidian <i>æstivo-autumnal</i> plasmodium. |

NOTE.—In this plate the tertian *æstivo-autumnal* plasmodium is shown. The staining reactions of the quotidian plasmodium are exactly similar.

PLATE I

FIG. 1

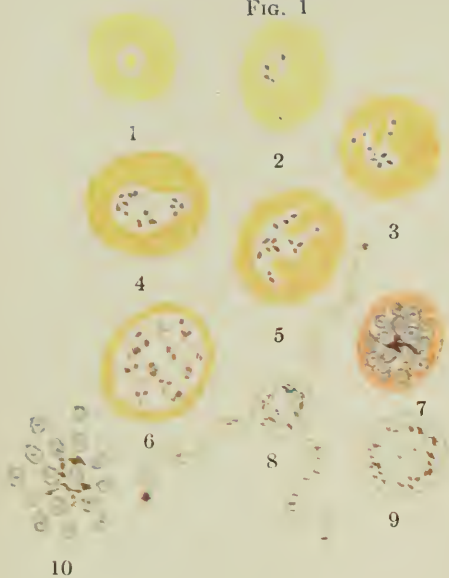


FIG. 2

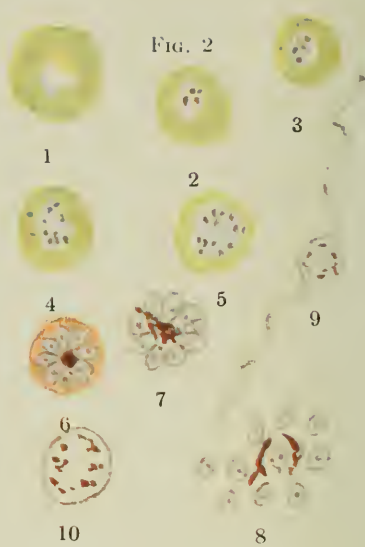


FIG. 3



FIG. 4

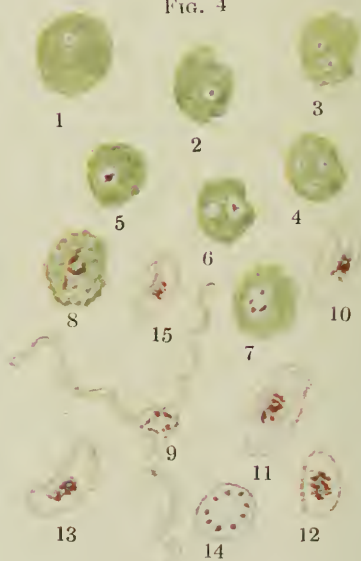


PLATE II

FIG. 1

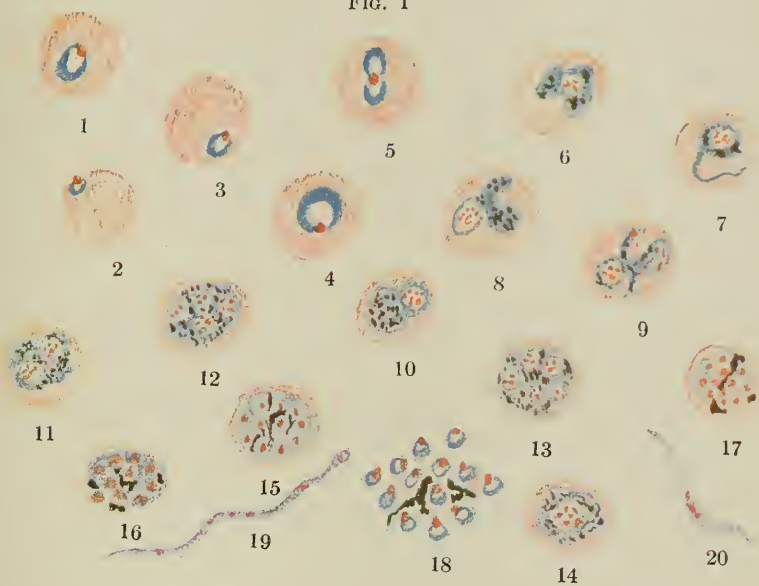


FIG. 2

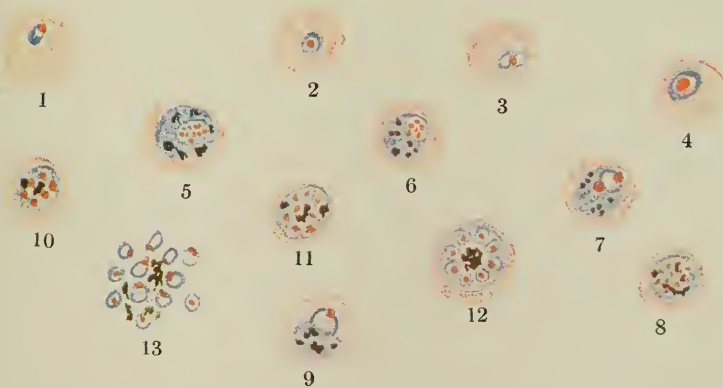
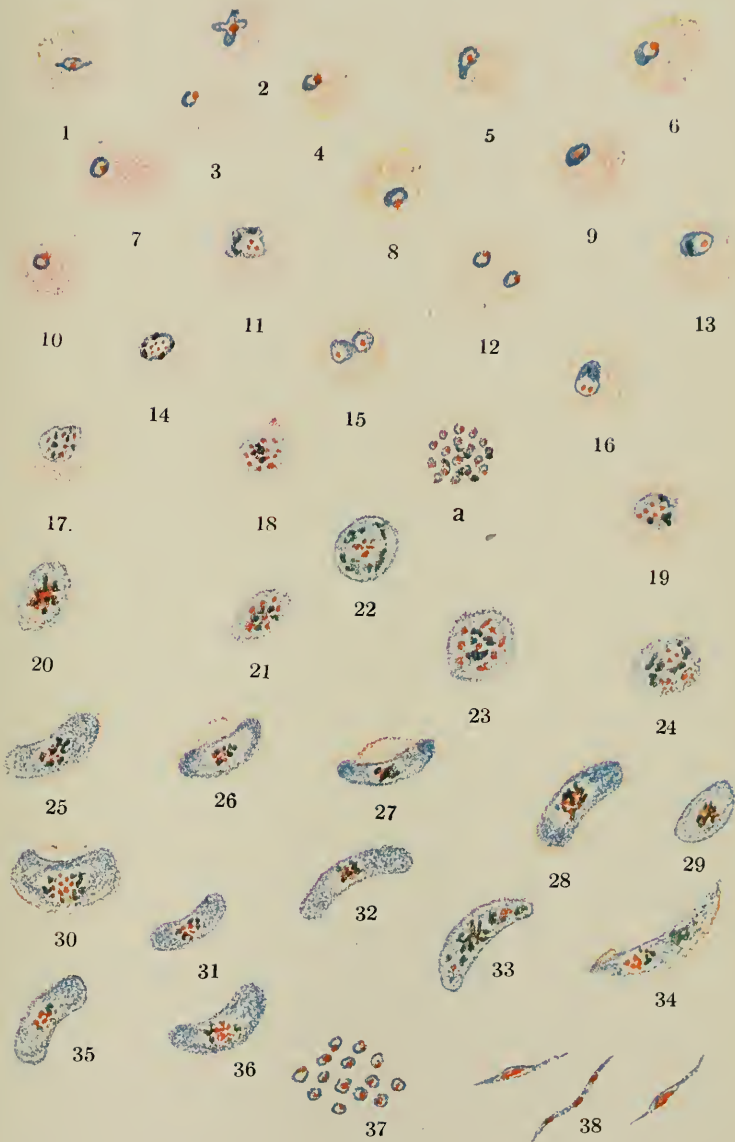


PLATE III



by the appearance of a few minute granules of reddish-brown pigment situated within it and showing active movement. This movement is due to protoplasmic currents which are present within the parasite. In the beginning, occupying but a minute portion of the red cell, as it continues to grow, the parasite encroaches more and more upon the infected corpuscle, until when full-grown it fills the entire cell. The growth of the parasite is gradual, covering forty-eight hours. The full-grown parasites have a rather distinct outline and the red cells containing them are greatly swollen, sometimes to almost double the size of the normal red blood corpuscle. Toward the end of thirty-six hours the organism has approached nearly to its full growth, only a narrow rim of the red cell showing around it. Amoeboid motion has become almost entirely lost, the parasite being circular in shape, well defined, the pigment more or less motile and much increased in quantity, still however, finely granular in appearance and reddish-brown in color. At the end of forty-eight hours segmentation takes place, the pigment becomes collected at the centre or to one side of the organism in the form of a compact clump and fine radial divisions are noticed branching from the centre toward the periphery of the organism, thus dividing the parasite into small ovoid segments. As a rule, there are two rows of these segments, one row surrounding the centre, and another surrounding the first row, but very often the segments are irregularly arranged, and they are always devoid of pigment. They vary in number from twelve to twenty-four, the average being about sixteen, and are known as *merozoites*. At the time that segmentation occurs the infected red cell has apparently disappeared, being entirely destroyed by the invading parasite. The destruction of the red cell, which is complete at the time of segmentation, liberates the segments, or *merozoites*, which are again capable of infecting new corpuscles, and thus the human life-cycle or schizogony continues. The pigment which is not present at the beginning of the life-cycle in the red blood corpuscle, gradually increases as the degeneration of the red cell continues, being derived from the destroyed hæmoglobin of the cell. In all the pigmented forms of the tertian parasite the pigment is generally motile, the movement being due to the protoplasmic currents which have been mentioned.

In examining blood from tertian cases it will be noticed that a certain proportion of the full-grown parasites do not segment, and it is these which are intended to commence the life-cycle of the organism in the mosquito, which will be described later.

Plasmodium Malarie—(The Quartan Parasite)—(Schizogony, Human Cycle).—Like the tertian parasite, the organism causing quartan malarial infection appears at first within the red corpuscle as a small actively amoeboid hyaline body without pigment, the *schizont*. It will be noticed that the amoeboid motion is less marked than in the case of the tertian organism. The quartan parasite rapidly becomes pigmented, the pigment being collected in larger granules than is the case in the tertian parasite, being less motile and arranged around the periphery of the organism, whereas in the tertian parasite the pigment is distributed throughout the protoplasm. The outline of the organism is also much more distinct than is the case in the tertian parasite during all stages of its growth. Instead of the swollen decolorized red cell seen in the tertian infection, the infected corpuscle in quartan fever is normal in size and often slightly

below normal, and darker green in color, instead of pale. This difference in the appearance of the infected red cell serves at once to distinguish the two varieties upon microscopic examination of the blood. The parasite slowly increases in size, and in doing so becomes less amoeboid. The pigment increases in quantity and becomes collected at the extreme periphery of the organism and is absolutely immotile. The granules of pigment are considerably larger than in the tertian parasite, darker in color, and at no stage of the growth of the organism do they collect in small clumps throughout the protoplasm, as is common in the tertian form. As growth increases the parasite tends more and more to fill the infected red cell, and when full-grown—that is, at the end of seventy-two hours, it almost fills the cell, a small greenish rim of hæmoglobin still being visible around the organism. At this stage of its growth the parasite is very distinctly outlined and is much more refractive than is the tertian variety; the pigment is absolutely motionless and collected around the periphery; the shape is circular and amoeboid motion has entirely ceased. At the end of seventy-two hours segmentation occurs, the pigment becoming collected at the centre or in a star-like arrangement distributed from the centre. Radial striations appear dividing the organism into from eight to twelve segments, or *merozoites*. The segments are generally arranged in a perfectly symmetrical manner around the central pigment, giving the so-called daisy or “Marguerite” appearance to the parasite at this stage. When segmentation is complete, each merozoite becomes free in the blood plasma and, in the human life-cycle, again invades the red corpuscles, undergoing the changes which have been described. As in the tertian form, certain parasites do not undergo segmentation, and these are the ones intended to carry on the life-cycle in the mosquito.

Plasmodium Falciparum—(Æstivo-Autumnal Parasite)—Quotidian Form—(Schizogony, Human Cycle).—As has been stated, the writer believes with Marchiafava and Bignami that there are two distinct varieties of the æstivo-autumnal parasite, the quotidian and tertian. These are distinguishable microscopically and the symptoms produced by them are characteristic and easily differentiated clinically. In previous contributions¹ the differential points between these two varieties of the æstivo-autumnal parasite and also the clinical phenomena which are produced by them have been described.

The *quotidian* parasite appears at first in the infected red cell as a very minute ring-shaped or round hyaline body, the *schizont*, which upon close inspection shows very active amoeboid motion. The outline of the organism at first is indistinct but gradually becomes more distinct and when full-grown it is very clear-cut and refractive. The round forms are perfectly hyaline in appearance but the ring form, which is most common, consists of a narrow hyaline body enclosing a small area which shows the normal greenish-yellow color of the infected corpuscle. This appearance is considered by most authorities to be due to the fact that the centre of the parasite is much thinner than the periphery, thus allowing the normal color of the corpuscle to show through. Careful observation of these ring forms, however, will show that they often become perfectly hyaline

¹ *The Philadelphia Medical Journal*, April 7, 1900; also, *Journal Am. Med. Association*, Nov. 3, 1900, *The Æstivo-Autumnal (Remittent) Malarial Fevers*, Wm. Wood & Co., 1901; *International Clinics*, vol. III, 13th series, Oct., 1903.

and in so doing the protoplasm of the organism flows in from the edge of the ring, thus tending to prove that no protoplasm existed in this greenish-colored area. The amoeboid motion is very active, but the organism has to be carefully watched in order to distinguish it. The infected red corpuscle is generally smaller in size than the normal corpuscle and darker green in color. It is very apt to be crenated. In many instances double or triple infections of the corpuscle may be observed. In the peripheral blood the hyaline, round or ring-shaped organisms are those which are most commonly observed, although a certain number of pigmented forms are not uncommon. The pigmentation is never as marked as in the tertian or quartan parasite, the pigment consisting of a small, solid block, almost black in color, situated at some portion of the edge of the parasite or at the centre; it is never motile. Very rarely the pigment consists of fine granules, but these granules never number more than three or four. The segmenting forms are but very seldom observed in the peripheral blood, although blood from the spleen taken at the proper time in well marked cases presents numerous parasites undergoing this process. Segmentation occurs at the end of twenty-four hours. Just before segmentation the parasite occupies about one-fourth of the red blood corpuscle, thus distinguishing it from the quartan and tertian varieties which fill the corpuscle. The pigment does not show any decided increase in amount and is absolutely immotile. At the time of segmentation this pigment becomes collected at the centre of the parasite and radial striations can be detected, starting from the centre and dividing it into from six to eight very minute round or oval segments, or *merozoites*. While in the tertian and quartan forms it is often impossible to distinguish the remains of the red corpuscle when segmentation occurs, in this variety it can be plainly seen that segmentation occurs within the infected red cell. The merozoites are liberated by the entire destruction of the red corpuscle; each merozoite is capable of again infecting the red cell and the human cycle is thus repeated.

In this variety, as well as in the tertian form, peculiar bodies occur which are developed within the red blood corpuscle, but which do not undergo segmentation. These are the so-called crescents, which are so characteristic of æstivo-autumnal infections, and which will be described in considering the mosquito-cycle of this parasite.

Plasmodium Falciparum—(Æstivo-Autumnal Parasite)—Tertian Form (Schizogony, Human Cycle).—Like the quotidian, the tertian æstivo-autumnal parasite appears first within the infected red cell as a round hyaline ring or disk. The infected corpuscle is greenish in color, smaller than the normal corpuscle surrounding it and generally crenated. The young parasites are considerably larger than the quotidian parasite, occupying from one-fourth to one-third of the total area of the infected cell. The ring forms are irregular in outline, one portion of the ring being larger than the rest, giving it the so-called “signet-ring” appearance. The organism is very highly refractive and sharply outlined, appearing as though it had been cut into the corpuscle with a punch. Amoeboid motion is present, although it is less rapid than in the quotidian form, and only very rarely is more than a single parasite seen within one corpuscle. In the course of from twenty to twenty-four hours the hyaline forms become pigmented, the pigment occurring in the form of very fine, reddish-brown

granules somewhat resembling those found in the tertian parasite. The pigment is in larger amount than in the quotidian parasite and is generally motile. As growth increases amœboid motion becomes lost, and this is also true of the peculiar ring-shape which is so characteristic of this form of the parasite. At the time of segmentation, which occurs in forty-eight hours, the organism occupies about one-half of the infected red cell. The pigment is collected at the centre and radial striations start from this point and divide the parasite into ten or fifteen segments, or *merozoites*. In some instances as high as twenty-four *merozoites* have been counted. Segmentation occurs within the red blood corpuscles but its situation is not so easy to distinguish in this form as in the quotidian. The segmenting forms occur but seldom in the peripheral blood, although they are very numerous in certain cases in blood collected from the spleen. The young segments are liberated in the blood plasma and again infect the red cell; thus the human cycle is repeated.

So far, we have considered the human cycle of the malarial plasmodia, which consists, briefly, in the infection of the red blood corpuscles by the merozoites which are derived from the segmenting bodies. The mosquito-cycle, which is more complex, will now be considered.

Development of the Malarial Plasmodia Within the Mosquito—(Sporogony, Sexual or Mosquito-Cycle).—Historical.—That malaria is transmitted by insects is by no means a modern conception. Nearly two thousand years ago, Varro and Columella mentioned the possibility that these diseases were transmitted in this way. In 1848, Nott¹ considered the subject as already proven, but King,² of Washington, in 1882, was the first to advocate it vigorously and give evidence in favor of this method of transmission. In 1884, Laveran³ considered the subject and suggested that this was probably the way that malarial disease was transmitted. In 1894, Manson⁴ elaborated the theory and stated it as his belief that malarial disease was transmitted probably by mosquitoes. In 1895, Ross,⁵ of the Indian Army Medical Service, studied the development of the parasites of æstivo-autumnal malaria in mosquitoes, and proved that the crescents underwent definite changes within the body of the insect. In 1896, Bignami⁶ advocated the theory that the malarial diseases were transmitted by the inoculation of man by the bite of the mosquito, comparing this process of infection to the one already proved in the production of Texas cattle-fever by the tick. In 1897, Ross⁷ further elaborated his experiments and was able to observe the development of the crescentic form of the æstivo-autumnal parasite in the mosquito. A great advance was made when MacCallum⁸ observed that the full-grown extracellular *halteridium*, a parasite causing avian malaria, consisted of two forms, one of which is flagellated and the other

¹*New Orleans Medical and Surgical Journal*, 1848, IV, 563, 601.

²*Transactions of the Philosophical Society of Washington*, February 10, 1882.

³*Traité des Fièvres Palustres*. Paris, 1884, pp. 457-458.

⁴*British Medical Journal*, December 8, 1894.

⁵*Proceedings of South Indian Branch British Medical Association*, December 1 1895.

⁶*Lancet*, November 14 and 21, 1896.

⁷*British Medical Journal*, December 18, 1897.

⁸*Bulletin of Johns Hopkins Hospital*, November 1897; also *Journal of Experimental Medicine*, January, 1898.

non-flagellated. He observed that the flagella, breaking away from the flagellated form, penetrated the non-flagellated organisms, and after penetration a motile body resulted which moved about among the blood corpuscles, and which was capable of penetrating and destroying them. Later he observed the same phenomena in studying the æstivo-autumnal parasites, and considered that this process was one of fertilization.

In 1898, Bignami performed some inoculation experiments upon man with mosquitoes which had bitten individuals suffering from malaria, but these experiments were unsuccessful, due to the fact that he did not employ the right species of mosquito. Later Bignami¹ was successful in producing an attack of æstivo-autumnal malaria in man by allowing mosquitoes which had bitten an infected individual to bite a patient who had never had malaria. In the same year, Bastianelli, Bignami, and Grassi² were successful in producing a double tertian infection in man by the bites of infected *Anopheles*. In February, 1899, they were, for the first time, successful in infecting the *Anopheles maculipennis* with quartan parasites, and traced the developmental stages of this organism in the mosquito. They were also successful in producing æstivo-autumnal malaria by the bites of infected mosquitoes.

Description of Forms Occurring in the Mosquito Cycle.—As has already been mentioned, in tertian and quartan infections there occur certain organisms which do not undergo segmentation. This is also true of the æstivo-autumnal infections, in which occurs a peculiar body known as the crescent, intended to continue the life-cycle of the parasite within the mosquito.

Tertian and Quartan Forms.—In tertian and quartan infections, in blood which has been removed from the body for some time, there occur peculiar bodies known as flagellated organisms. It will be noticed that these bodies are of two kinds, which the writer designated in a previous contribution³ as active and passive flagellated organisms. The active flagellated organism, or the *microgametocyte*, is spherical in shape and filled with actively motile pigment. This pigment is in the form of small granules which are distributed throughout the protoplasm of the organism. It will be noticed that in such round bodies the pigment becomes more and more active, until finally three or more serpentine prolongations of the protoplasm appear at the circumference of the organism. These prolongations of the protoplasm are from three to four times the diameter of the parasite and are possessed of a very active lashing movement, and are known as flagella, or *microgametes*. Together with this form of the organism there occur round bodies in which the pigment is collected in larger clumps and generally arranged around the circumference in the form of a perfect ring, while there is no evidence of motility. These are the passive flagellated organisms, or *macrogametes*, and never present the process of flagellation as seen in the *microgametocyte*, or active body. The flagella from the *microgametocyte* eventually become free in the blood plasma and sometimes can be seen attached to the bodies which have just been described, *i.e.*, the *macrogametes*. This process, however, takes place in nature

¹ *Lancet*, December 3 and 10, 1898.

² *R. Acad. dei Lincei*, vol. VII, Dec. 4, 1898.

³ *New York Medical Journal*, December 23, 1889.

in the middle intestine of the mosquito. A distinct difference has been demonstrated in the structure of the female *macrogametes* and the male *microgametocytes*. In the *macrogamete* the nucleus is of good size and situated at one side of the centre of the organism, containing little chromatin. In the *microgametocyte* the nucleus is always situated at the centre of the organism and contains a large amount of chromatin. When the flagella, or *microgametes*, develop from the *microgametocyte*, it has been demonstrated that the chromatin passes into them and forms an essential portion of their structure.

Æstivo-Autumnal Infections.—There occur in the blood in æstivo-autumnal infections peculiar forms of the parasite known as crescents. These forms are developed within the red blood corpuscle and are typically crescentic in shape. They are very refractive, having a more or less granular protoplasm, and contain within them, generally at the centre, but sometimes at one or the other pole, a clump of pigment arranged in the form of slender rods or minute dots. In the very young crescents the pigment is distributed throughout the protoplasm, but as the crescent matures it collects at the centre or at one end. The border of the crescent is sharply cut and is represented by a single or double line, having a peculiar greenish color. In most crescents, when full-grown, careful examination will show a dim line upon the concave side of the organism, which has a peculiar greenish color. This represents the remainder of the red blood corpuscles in which the crescent was developed.

In tertian æstivo-autumnal infections the crescent is much more slender and has pointed extremities. It very seldom shows a double outline; the protoplasm is finely granular and the pigment is large in amount and in the form of slender rods. In the quotidian æstivo-autumnal infections the crescent is generally much shorter and plumper than in the tertian. Its extremities are rounded and it always presents a distinct double outline. The protoplasm is less granular and the pigment is smaller in amount and in the form of dots. Normally in the mosquito, and also in the blood which has been removed for some time from the body, these crescents undergo a series of changes, first becoming oval in shape and finally round. The spherical bodies represent, in the æstivo-autumnal infections, the *macrogametes* and *microgametocytes* of the tertian and quartan infections and undergo similar changes in the stomach or middle intestine of the mosquito; that is, the male elements, or *microgametocytes*, become flagellated, the flagella, or *microgametes*, becoming free and fertilizing the female elements, or *macrogametes*.

Cycle of Development.—Having considered the bodies which enter into the mosquito-cycle, and which may be observed at times in human blood which has been removed from the body for a short time, we will now take up the cycle of development which these bodies undergo in the mosquito, bearing in mind that it is essentially the same in all varieties of the plasmodia. The process of flagellation and the fertilization of the *macrogamete*, the female organism, by the *microgamete*, or flagellum, which occurs normally in the middle intestine of the mosquito after biting an infected individual, has been described. The result of this fertilization is known as the *sporont*. After a certain period of time the *sporont* becomes elongated and finally motile, and it is then known as the *ookinete*. The *ookinete* penetrates the wall of the middle intestine and eventually becomes situated on the outer

side of the epithelium and the basement membrane of the intestine between the adipose tissue and the muscular wall. Here the organism becomes spherical in shape and forms a cyst known as the *oocyst*. At this stage the protoplasm is granular and reticular in appearance, the pigment is reduced in amount, and the entire organism is enclosed within a well-defined capsule. The *oocyst* is formed at about the third or fourth day after infection of the mosquito. About the fifth or sixth day the *oocyst* enlarges and within it are formed spherical refractive bodies known as *sporoblasts*. At this stage the organism is increased so much in size that it projects from the intestinal wall. Besides the *sporoblasts*, the cyst contains some pigment and minute granules which resemble fat. At the end of a week the *sporoblasts* have produced a large number of delicate filaments having pointed extremities and containing a small amount of nuclear chromatin. These filaments are the *sporozoites*. They are about 14μ in length and are arranged in a ray-like formation about a central mass which may contain pigment. At this stage the capsule of the cyst is very distinct. The *sporozoites* are finally liberated by the rupture of the cyst and make their way to the tubules of the salivary glands. At this time the infected mosquito, when biting a man, will inoculate the *sporozoites*, which, penetrating the red blood cells, develop into *merozoites*, and the human cycle of the organism begins. The entire cycle of development in the mosquito is about fourteen days in duration.

Briefly stated, the cycle of development of the malarial plasmodium in the mosquito may be summed up as follows:

1. *Macrogamete*, in tertian and quartan infections, the female spherical bodies, and in æstivo-autumnal infections the female crescent.
2. *Microgametocyte*, in tertian and quartan infections the male spherical bodies and in æstivo-autumnal infections the male crescent.
3. *Microgamete*, the liberated flagellum of the *microgametocyte*.
4. *Sporont*, the result of the fertilization of the *macrogamete* by the *microgamete*.
5. *Ookinete*, the motile stage of the *sporont*.
6. *Oocyst*, the cystic stage of the *sporont*.
7. *Sporoblasts*, developed within the *oocyst*.
8. *Sporozoites*, developed within the *sporoblasts* and liberated by the rupture of the *oocyst*, and which are introduced into man by the mosquito and are capable of beginning the human life-cycle by infecting the red blood corpuscles.

It may be stated that this cycle of development has been demonstrated in the mosquito in all varieties of the malarial plasmodia, and that infection of man by the mosquito has also been demonstrated with all varieties of the plasmodia.

The Malarial Mosquitoes.—The structure and habits of the mosquitoes which transmit malaria have been considered in another portion of this work. It may not be amiss to give a list of those mosquitoes which have been proved to transmit malarial disease. Only one genus, so far as we know, is capable of transmitting malaria, the *Anopheles*. Of the fifty or more described species belonging to this genus, the following have been shown experimentally to transmit the disease:

In Africa, the *A. costalis*, *A. paludis*, *A. fuscus*.

In India, *A. sinensis*, *A. Rossii*, *A. culicijacis*, *A. Theobaldi*, *A. barbirostris*.

In Europe, *A. superpictus*, *A. maculipennis*, *A. bifurcatus*.

In America, *A. maculipennis*, *A. argyrotarsus*.

Staining Reactions of the Malarial Plasmodia.—Under the division of this subject dealing with diagnosis, the staining methods which are of greatest practical use will be fully discussed. While the examination of the fresh blood is of the greatest importance in studying certain phases of the life-cycle of the malarial plasmodia, the staining reactions exhibited by these organisms illustrate more fully the exact morphological structure. It may be stated that the staining reactions are similar in all varieties, and that they prove that the organism is composed of a nucleus and protoplasm. The chromatin is the only portion of the nucleus which takes the stain, and by Wright's method it stains a very brilliant red and lies, apparently, within a vesicular nucleus, the protoplasm of which does not stain. Surrounding the nucleus in the young forms is a small amount of protoplasm which stains a delicate blue color, and imbedded in which is the pigment. In all the forms, as the parasite matures, the chromatin becomes distributed throughout the protoplasm, and in the full-grown parasites a distinct nucleus cannot be demonstrated, while the protoplasm stains uniformly throughout. As segmentation approaches, the pigment becomes collected more or less toward the centre of the organism, and the chromatin which has been distributed diffusely throughout the protoplasm collects into small clumps, forming a portion of the young segments. At the time of segmentation the chromatin is compactly collected in clumps lying within a minute unstained area, the vesicular portion of the nucleus, and surrounded by a small ring of protoplasm, staining very intensely. In the æstivo-autumnal infections the crescents are composed, as shown by the staining reactions, of a large amount of protoplasm and a compact clump of chromatin situated at the centre or at one pole of the crescent. The flagellated organisms stain similarly to the full-grown parasites with the exception that a narrow thread of chromatin can be detected within each flagellum. This chromatin gradually becomes collected toward the centre of the flagellum before it becomes free from the parent body, the remainder of the flagellum staining a uniform blue, the chromatin being bright red in color. There are many exceptions to this general rule regarding the staining properties of the plasmodia, but these are probably due to external factors.

In all varieties of the malarial parasite the first stage seen within the red cell in stained specimens is ring-shaped, consisting of a small dot of chromatin surrounded by an unstained area, and this again surrounded by a small amount of protoplasm.

Contributing Factors in Etiology.—While the malarial parasites, or *hæmosporidia*, are the direct cause of the malarial infections, and while the transmission of the disease depends entirely, so far as we at present know, upon mosquitoes of the genus *Anopheles*, there are certain factors which enter indirectly into the etiology of the disease. These factors favor the development of the parasites within the body or indirectly aid in infection. Among them may be mentioned the following:

Locality.—This subject has already been considered under the geographical distribution of malaria but it has a decided influence upon the

character of the infection. The mild tertian and quartan infections, especially the tertian, are of almost world-wide distribution, but the more severe æstivo-autumnal types are much more limited as regards locality, being very uncommon in northern latitudes and becoming more and more common as the tropics are approached.

Climate.—As stated in the foregoing, climate has a decided influence as regards the distribution of certain types of malarial infection. These infections are most common and pernicious in tropical climates, so that heat may be considered as an essential predisposing cause of the malarial fevers. Even in temperate climates, the æstivo-autumnal fevers prevail mostly during the summer and autumn months, while in the tropics they prevail throughout the year. Thayer and Hewetson¹ call attention to the seasonal variation of these diseases as observed in Baltimore. The smallest number of cases occurred during the months of December, January and February; during the spring months the cases increased until May, and then decreased until July, when they again increased and reached the maximum in September. The observations of these authorities have been borne out by those of numerous investigators, and there can be no doubt that the season has a most marked influence as regards the number of cases observed in any locality. This, of course, is probably due to the fact that mosquitoes, especially in temperate climates, are much more numerous during the spring, summer, and autumn months.

Time of Day.—It has always been observed that there is much more danger of contracting malaria at night than during the day. In the light of our present knowledge that these diseases are due to inoculation by the bite of the mosquito, this fact is easily explained, for it is during the night that mosquitoes mostly bite.

Altitude.—These diseases occur especially in low-lands along the coast and rivers of warm countries. This is a fact which has been observed since the very earliest study of malarial infections. Mountainous regions are generally free from malaria, although this is not always so, for in the Philippine Islands certain valleys are almost free from malaria, while the hills in the vicinity are notoriously infected. It has also been observed that persons living in the tropics and sleeping in the lower stories of houses are more apt to become infected with malaria than those in the upper stories. For a long time this was held to be due to low-lying noxious vapors which penetrated the lower floors but did not rise to the upper stories of dwellings. The true explanation is that, as a rule, mosquitoes do not fly to any great height.

Moisture.—Marshes and low-lying damp regions are usually conducive to malaria, and moisture is a most important factor in the distribution of the disease. This is again explained by the fact that mosquitoes are most numerous and breed most abundantly in moist regions.

Soil.—It was long ago observed that the sailors upon ships cruising in tropical regions did not contract malaria unless they went on shore, and it was supposed that the miasmatic gases arising from swamps and moist soil led to the production of the disease, and for a long time it was believed that the upturning of the soil in certain regions led to an outbreak. Tropical jungles, low marshy islands, or lands covered with pools of stag-

¹ *Johns Hopkins Hospital Reports*, Vol. V, 1895, pp. 5-215.

nant water have always been regarded as conducive to malarial infection. The fact remains, however, that the soil *per se* has nothing to do with the production of malarial disease except in so far as it favors the breeding of mosquitoes. A moist soil favors the spread of the disease as it brings about the conditions favorable for the development of the mosquito larvæ; this is also true of those instances in which malarial epidemics have followed the upturning of soil in certain localities, thus favoring the formation of stagnant pools in which the larvæ of the mosquito develop.

Rain.—Rain favors the production of malaria because it favors the breeding of the mosquito. Added to this, continued rainy weather, by diminishing the resisting powers of the individual, favors the development of the disease after he has become infected by the mosquito.

Race.—According to Thayer and Hewetson, the negro is less liable to contract malaria than the white man. This subject has attracted the attention of a great many investigators, and it has been found that the native negro races acquire a more or less complete immunity in early life from malarial disease. A very large percentage of negro children in infected localities are found to harbor the malarial plasmodia, but this is not true of the adult. There is probably no racial immunity against malaria, but it is undoubtedly true that an acquired immunity is present among many people who inhabit malarial regions.

Age.—Children are more susceptible to malarial infection than adults, and, as has been suggested by Marchiafava, this is probably due to the fact that mosquitoes bite children in preference to adults.

Sex.—When equally exposed, both sexes have the same ratio of infection, but, as a matter of fact, malaria is more common in men than in women, as the latter are not as often exposed to the bites of the mosquito.

Occupation.—The occupation of man becomes a predisposing factor in the production of the disease in proportion to the chances that occupation gives him of infection by the mosquito. Laborers working at ditching, railway building, and other occupations which necessitate the turning up of the soil and exposure to night air, and therefore to the bites of mosquitoes, are especially liable to contract the malarial fevers. An instance of this was the terrific mortality from æstivo-autumnal malaria during the early work upon the Panama canal.

There are numerous other factors which contribute to the production of malarial fevers, among which may be mentioned those which lower the individual's resisting powers, such as exposure, dissipation, over-eating, over-work, whether mental or physical, and, in short, anything which interferes with the normal physiological processes. There can be no doubt that an infection with a small number of malarial parasites is overcome, in a great many instances, by the healthy individual, but should the normal resisting powers be lowered such an infection would result in the symptoms of the disease.

Cultivation.—No one, as yet, has been able to cultivate the malarial plasmodia in artificial media, outside of the human body. The only investigator who has ever claimed to have done so is Coronado,¹ but his experiments have been repeated by other observers, none of whom has been able to confirm them. While cultivation of these organisms has not

¹ *Cronica Medici Suirurgica de la Habana*, November, 1892.

been successful, the æstivo-autumnal parasites have been kept alive outside of the human body for some days. Sakharov was the first to perform such experiments and he was able to keep the parasites alive in blood, obtained by leeches from the human subject, for a week. No reproductive changes, however, were observed. Hamburger and Mitchell, as quoted by Thayer,¹ performed similar experiments and were able to keep the æstivo-autumnal parasites alive for a period of eight days.

Inoculation Experiments.—The malarial fevers may be transmitted by direct inoculation from man to man. It would be unprofitable here to detail the experiments which have been performed along this line, but the disease has been successfully reproduced in this way by Gerhardt, Mariotti, Marchiafava, Celli, Bignami, Bastianelli, Baccelli, Sakharov, Elting, and many others. It has invariably been found that the type of parasite inhabiting the blood injected is found again in the blood of the individual infected, and is followed by the clinical symptoms of the variety of malaria produced by the type of parasite injected. Thus, for instance, the inoculation of blood from a patient suffering from tertian fever is always followed by tertian fever in the inoculated individual.

Immunity.—This may be considered under the following heads, racial, congenital, and acquired immunity. Natural immunity may occur, but it is undoubtedly rare.

Racial Immunity.—Certain races of mankind have been considered immune to the malarial fevers. This statement, however, rests upon but very little proof, and cannot be substantiated by facts. While this is so, it is a well-recognized fact that some races are more resistant to malaria than others. For instances, the black races are more resistant in adult life, but the immunity which exists is possibly acquired. In other words, in those races which live in malarial localities the disease is acquired in very early life and a natural immunity is established so that the adult individuals are resistant to the infection. It may be stated as a fact that no people inhabiting the world are, as a race, immune to the malarial fevers.

Congenital Immunity.—There exist people, living in the most malarious localities, who have never suffered from the disease. This immunity is, in all probability, congenital, and in a few instances has been proven to be a family characteristic.

Acquired Immunity.—Long residence in malarious country may, if the individual survives, confer upon him a relative immunity to the disease. Repeated attacks of malaria will in time render the individual less liable to further attacks. We can explain this in only one way: that the malarial poison produces certain changes in the human organism which render it at least partially immune to future attacks. The history of acquired immunity is simply that of repeated attacks of malarial fever, each one a little less severe than the preceding, until at last a spontaneous permanent cure is affected. Such immunity may be lasting, but as a rule hardship, privation, ill-health, or removal to a new locality will destroy it.

Pathology.—Primarily, malarial infections exert the most marked effect upon the blood, as the plasmodia live at the expense of the red blood corpuscles, and probably elaborate toxins which materially affect all the ele-

¹*Lectures on the Malarial Fevers*, 1897, p. 27.

ments of this fluid. In 1847, Meckel discovered granules of pigment in the blood, and ever since then the condition of melanæmia has been recognized as one of the most characteristic features of malarial disease. It may be stated that the pathological changes which occur in the blood are the result of primary and secondary causes, the primary cause being the infection of the red cells by the parasites and the changes brought about by such infection; the secondary, the anæmic condition which is the inevitable result of malarial infection.

Changes in the form of the red corpuscles are always present, as in tertian infections, where the corpuscles are swollen and much larger than normal, while in the æstivo-autumnal infections they are smaller, the color is much darker and the corpuscles appear greenish or brassy in color. Many of the infected red corpuscles, especially in the æstivo-autumnal infections, show a retraction of the hæmoglobin, small areas being thus rendered colorless. The infected red cells are gradually destroyed by the growth of the parasite within them, but even in those which are not infected a marked difference is noted in the color index and in the form.

There occur in the blood macrophages, containing much pigment, and in the æstivo-autumnal infections especially, numerous plasmodia. Together with these there occurs either free or within many of the leukocytes, brown, black, or brownish-yellow pigment, occurring as blocks, granules, rods, grains, and irregular clumps. The occurrence of this pigment is one of the most characteristic conditions found in the blood of malaria. The pigment occurs in two forms, *melanin* and *hæmosiderin*. The first gives no reaction for iron, while the second does. As regard the origin of the two varieties Bignami has well said:

"The melanæmia, index of an acute infection, is derived only from the direct transformation of hæmoglobin into *melanin* through the action of the parasites within the red blood corpuscles; the melanosis of the viscera, spleen, liver, bone-marrow, etc., index of a previous infection, has a double origin. In chief part it is derived from the melanæmia; that is, from the deposition in the viscera of the black pigment (*melanin*) formed during the acute infection in the circulating blood; in part it has a local origin, that is, it is derived from the slow transformation of the blocks of yellow-colored pigment (*hæmosiderin*), which are deposited or formed in the spleen and in the other viscera from the enormous quantity of altered red blood corpuscles, which, in grave infections, die before the direct action of the parasites has transformed their hæmoglobin into black pigment."

Besides the occurrence of changes in the form and color of the red blood corpuscles, as well as the occurrence in the blood of pigmented leukocytes and pigment, in all forms of malarial fever there is a reduction in both the red and white corpuscles. This reduction is very often more marked in tertian and quartan malaria than in æstivo-autumnal and is due to the action of the parasites upon the corpuscles containing them, the action of the poisonous material elaborated and set free by the parasites, and to inhibited function of the blood-producing glands.

Most valuable observations upon the reduction of the red cells have been made by Kelsch,¹ who found that a reduction followed every

¹ *Archives de physiologie*, 1875, 690.

paroxysm of the fever. This reduction may be very great; some cases have been observed in which only 500,000 red cells were present to the cubic millimeter. In ordinary cases, after the infection has persisted for a few days, it will be found that the red cells have fallen to 2,000,000, or slightly less, per cubic millimeter. This marked reduction, however, is not persistent, for in long-continued infections it will be found that after a certain amount of anæmia has been produced there is no further fall, and even in most cases a slight gain over the lowest point reached during the acute infection. In the pernicious forms the red cells may fall to 1,000,000 or less per cubic millimeter within twenty-four hours, but if the patient has suffered from repeated attacks such a marked decrease is but seldom observed. The return to the normal number of red cells is generally rapid after the mild, and in some cases after severe infections which have been promptly stopped by treatment; but in cases which have been treated improperly or where many relapses have occurred a chronic and persistent anæmia is produced which is one of the most marked characteristics of chronic malarial infection.

As regards the white corpuscles, it may be said in general that the reduction in their number corresponds with that of the red cells. During the paroxysm there is often a leukocytosis, while between the paroxysms the leukocytes are markedly reduced in number. This is, in general, true of all forms of malarial fever, but in some cases of fatal pernicious malaria a leukocytosis is observed, which is a strong argument against the theory of Metchnikoff that the leukocytes play the most important part in the spontaneous cure of these infections. Recently much attention has been paid to the relative increase in the mononuclear leukocytes as being of diagnostic importance in malarial infection. While probably in a majority of instances there is a considerable increase in this type of cell, it has not been the writer's experience that very much weight can be given in diagnosis to a mononuclear increase in malarial infection.

Besides the reduction in the red and white corpuscles there is generally a marked reduction in the hæmoglobin, especially in the æstivo-autumnal infections. This reduction may be very rapid, the hæmoglobin falling from 10 to 40 per cent. within two or three days. But little weight can, however, be given to the reduction of the hæmoglobin as regards the prognosis of individual cases. In some of the most pernicious forms of malaria there may be but a slight reduction in hæmoglobin, while in many benign tertian infections there is often a very marked reduction.

Summing up our knowledge as regards the changes in the blood in the malarial fevers, it may be briefly stated as follows: A marked reduction of the red cells both by parasitic infection and as the result of poisons elaborated by the parasites, as well as changes brought about by these poisons in the blood-forming glands; a corresponding reduction in the number of white cells, with, in most cases, a relative increase in the mononuclear leukocytes; a marked reduction in the hæmoglobin, and the presence in the blood of more or less black and brownish-yellow pigment.

The chief changes in the blood of patients who have suffered from repeated attacks of malaria consist in a greater or less degree of anæmia, the red blood cells seldom numbering more than 3,000,000 per cubic millimeter, often not over 1,500,000, and a reduction in hæmoglobin and the leukocytes.

In severe cases nucleated red cells are sometimes seen and poikilocytosis is almost invariably present. In such cases the polymorphonuclear leukocytes are decreased while the mononuclear are increased.

The Urine.—In many cases of benign tertian and quartan malarial infections there is but little change in the urine, but in the more severe æstivo-autumnal infections there is often a marked reduction in the amount during the apyrexial stage, while during the paroxysms the amount is increased. *Polyuria* is often marked during the convalescence from tertian and quartan fevers but is not so common in the æstivo-autumnal infections. Sometimes the polyuria is very excessive. One patient observed by the writer, after a tertian æstivo-autumnal attack, passed from 20,000 to 25,000 Cc. of urine per day. The *color* of the urine is generally dark amber or reddish, as in other febrile diseases, and the *acidity* is increased when the urine is diminished in amount. The *specific gravity* is increased during the attack, but in cases showing polyuria it is generally very low, being from 1.005 to 1.010. The *total solids* are increased. The amount of *urea* excreted in twenty-four hours is increased, especially during the paroxysm, but in cases showing polyuria the amount is generally decreased. The *chlorides* are not increased as a rule. *Albumin* appears in a certain proportion of very severe tertian and quartan infections and in the majority of æstivo-autumnal infections. In the latter class of cases hyaline and granular *casts* are often observed, and it can be stated as a rule that all fatal cases of malaria show albuminous urine containing casts prior to death. Personal observations suggest that *indican* is almost invariably increased in the urine of patients suffering from æstivo-autumnal infections.

The Viscera.—The pathological changes occurring in the viscera have been thoroughly studied by many observers, among whom may be mentioned Bignami, Laveran, Councilman, Bastianelli, Dock, Thayer, Barker and Ewing. From the observations of these authorities, we have come to realize better the extensive pathological ravages of malarial infections. It should be understood that any of the malarial parasites may cause pernicious infections leading to the death of the patient, and the pathological changes produced by them do not differ markedly one from the other.

A patient dead of malarial fever presents a peculiar brown or grayish hue of the *skin*. The degree of emaciation depends upon the duration of the infection. Rigor mortis is moderate, and postmortem discoloration occurs early and may be very intense. As most cases of pernicious malaria die from cerebral complications, the *brain* presents most marked pathological lesions. Externally the bloodvessels are much congested, the entire organ appearing hyperæmic. Small capillary hemorrhages are often observed and œdema is the rule. In cases where no brain symptoms have been exhibited during life, the organ externally shows but little hyperæmia. The changes in the brain consist in congestion of the capillaries and the presence of minute hemorrhages within the substance of the organ. The congestion and hemorrhages are due to blocking of the capillaries by malarial parasites, which may be observed in various stages of development within the red cells, together with an immense amount of pigment and numerous pigmented leukocytes. Very often the pigment is present in such large amount that the organ appears pigmented upon

naked-eye inspection. The parasites may be so numerous that there are hardly any uninvaded corpuscles seen, or they may be few in number. Microscopically, it may be found that many of the capillaries in the severe infections are entirely filled with red cells containing parasites, and often thrombi are formed, composed of such corpuscles, together with pigment and pigmented leukocytes. Besides the infected blood corpuscles free parasites may be observed, as well as macrophages, free pigment, pigmented leukocytes, and endothelial cells. To the observations of Marchiafava and Monti we are indebted for valuable information upon the changes taking place in the nerve cells as the result of æstivo-autumnal infection. The changes occur both in the protoplasm and nucleus of the nerve cell and lead to a complete degeneration and consequent destruction of the diseased tissue.

Guarnieri has contributed a valuable research regarding the changes occurring in the *retina* in pernicious malaria, finding that they consist in hemorrhages and congestion of the capillaries, thus leading to impairment of function.

The changes in the lungs are not at all characteristic, varying considerably according to the stage of the disease, and being those usually found in severe fever. A microscopic examination of sections in certain cases shows congestion of the alveoli, which contain large numbers of pigmented, parasite-laden, white cells, and infected red blood corpuscles. In those cases in which bronchopneumonia has occurred, the exudation in the alveoli is mostly composed of polymorphonuclear leukocytes, together with numerous infected red blood corpuscles and pigment, although the free pigment is generally small in amount. A pneumonia complicating a fatal attack of malarial infection, is without doubt due to a double infection by the diplococcus of pneumonia and the malarial plasmodium.

No changes which are characteristic are observed in the heart muscle.

There has been considerable discussion regarding the changes occurring in the *stomach* and *intestine* in pernicious malaria. In certain cases in which diarrhœa has been marked some time before death, the mucous membrane of these organs is more or less pigmented and there is marked hyperæmia, and even necrosis and ulceration. The Peyer's patches, as well as the solitary glands, are often swollen. Upon microscopic examination, sections of the stomach and intestine show that the capillaries of the mucous folds are often crowded with parasite-invaded corpuscles and these may occlude the capillaries, resulting in necrosis and ulceration of the mucous membrane. The epithelial lining of the mucous membrane is often necrotic, and there may be present a general superficial necrosis of this portion of the membrane.

The liver is generally enlarged and markedly pigmented and in some cases it is almost black in color. Upon section, the cut surface is often very much pigmented and generally greatly congested. Microscopically the most marked changes are found in the capillaries and liver cells. The capillaries show many very large phagocytes containing much pigment and sometimes infected red blood corpuscles, as well as malarial parasites. The epithelial cells are greatly swollen and may contain free pigment and degenerated organisms. Free pigment is often observed in large lumps within the liver capillaries, while the stellate cells of Kupfer present marked pigmentation. The liver cells are atrophied, undergoing

fatty degeneration, necrosis and pigmentation. The pigmentation, however, in the liver cells, is not due to the malarial pigment but to pigment derived from degenerated red blood corpuscles and is not characteristic of malaria, as it occurs in many other diseases. One of the most characteristic and important changes occurring in the liver are areas of focal necrosis, which are believed by Flexner to be due to the presence of some circulating toxic substance.

The organ which presents probably the most marked changes in malarial infections is the *spleen*. It is almost invariably enlarged, sometimes enormously so. It is of a dark blue or almost black color externally, the capsule being smooth, while upon section the cut surface is of a chocolate, slate or almost black color, the consistence being very greatly decreased. The Malpighian corpuscles are almost invisible. Upon microscopic examination the capillaries are found greatly congested by multitudes of red blood corpuscles, most of them containing parasites. This is not always true, as there are numerous cases in which few infected red blood corpuscles are demonstrable in the spleen. The intense congestion of the capillaries pushes apart the cells of the splenic pulp, and in some cases large areas are destroyed by hemorrhagic exudation. In the spleen the red cells contain parasites in all stages of development, but the pigmented forms and the segmenting bodies are most commonly observed, as well as the crescents in æstivo-autumnal infections. Besides the infected red blood corpuscles, sections of the spleen show an immense number of phagocytes. These leukocytes consist of small cells which resemble lymphocytes, and larger cells known as macrophages. The macrophages contain clumps of pigment, red blood corpuscles containing parasites, free parasites, degenerated red blood corpuscles, and even the small phagocytic cells which have been mentioned. The Malpighian bodies do not become pigmented but the fibrous trabeculae always present marked pigmentation. The free pigment is present in the form of small rods or granules. Here, as in the liver, two forms of pigmentation occur, the dark brown or nearly black melanin, the malarial pigment, and the golden yellow pigment, or hæmosiderin, derived from degenerated red blood corpuscles.

The *kidneys* in pernicious malaria present very marked lesions which have been studied especially by Ewing and Dock, who have contributed very valuable work upon this subject. The condition produced is generally that of an acute nephritis, presenting all the typical lesions of this disease, together with the peculiar lesions due to malarial infection. As in the liver and spleen, microscopically the most marked change is the great congestion of the capillaries of the Malpighian tufts and the intertubular capillaries. These vessels are filled with infected red blood corpuscles, free pigment and pigmented leukocytes. There is also present a marked pigmentation of the endothelial and epithelial cells, as well as those lining the tubules. Free parasites are often observed and may be seen occasionally within the glomerular capillaries. The epithelium of Bowman's capsule is undergoing marked proliferation and the capillary space may be entirely occluded. The epithelium of the tubules presents marked degenerative changes, consisting of fatty and albuminoid degeneration and necrosis. The straight tubules often contain hyaline, epithelial or granular casts. It should be remembered that there is not a marked

pathological condition of the kidneys present in every case, but it is safe to say that most cases of pernicious malaria are accompanied by an acute parenchymatous nephritis presenting the peculiar lesions which have been described.

In certain cases the *bone marrow* presents very marked changes. Microscopically, unless the malarial infection has persisted for a long time, there is but little change. If weeks or months have elapsed, however, the color of the bone marrow changes from the normal yellow to red or dull black. The capillary vessels are found to contain numerous endo-corpuseular parasites in various stages of development, and in æstivo-autumnal infections, crescentic bodies. They also contain numerous macrophages, and in the marrow-pulp are found free parasites in various stages of development, as well as macrophages, nucleated red blood corpuscles, and pigmented medullary cells.

In considering the pathology of malarial infections it should be remembered that all the changes described are not presented, as a rule, in every case. Some cases will present marked changes in the spleen and liver, while the brain and kidneys are but slightly affected, and in others all the chief viscera of the body will show marked lesions. The pathology of chronic malarial infections, or malarial cachexia, is characteristic. As has been stated, there is always a marked anæmia, the spleen is greatly enlarged, sometimes weighing ten or more pounds, and presents marked pigmentation. The liver is also enlarged but not in proportion to the enlargement of the spleen. This organ also appears pigmented. The kidneys are enlarged, and grayish in color, due to deposits of malarial pigment. This is also true of the brain cortex, and upon section of the brain there is marked congestion of the capillaries, which contain numerous infected red blood corpuscles, pigmented leukocytes and free pigment. The condition present is characterized by the marked pigmentation of all the viscera, to which the name melanosis may well apply.

Pathology of Latent Malarial Infection.—The pathology of acute and chronic malarial infection having been considered, it remains to discuss the pathology of latent infections. By this term we mean those cases in which no symptoms of malaria are presented, but which have died from some other disease. During the last three years at the U. S. Army General Hospital, Presidio of San Francisco, California, seven cases have been observed in which the autopsy showed latent malarial infection; during life no symptoms of such infection had been presented. In three of these the infection was tertian in character, and in four, æstivo-autumnal. The pathology of these cases is interesting in that during life they presented no symptoms of malaria, and as showing the lesions produced before the disease could be diagnosed. The pathological lesions found were confined entirely to the spleen and liver. The spleen in the tertian infections was considerably enlarged and somewhat pigmented. Microscopically the sections showed intense congestion of the sinuses, together with pigmentation, especially marked along the edges of the Malpighian bodies and the fibrous trabeculæ. Many of the cells of the splenic pulp were pigmented. In the splenic sinuses and in the capillaries there were numerous parasite-infected red cells and pigmented leukocytes, but such cells were not nearly as numerous as in acute infections. The parasites were characteristic of those occurring in the peripheral blood and were all

in about the same stage of development in each case. While this was so, it happened that the patients died at such intervals that the entire human cycle of the tertian parasite could be worked out from an examination of sections of the spleen, and the chief point of importance in the pathology of latent infections, as observed in these cases, is that the entire human cycle of the parasite can be followed in the spleen when no parasites are demonstrable elsewhere in the body, thus proving conclusively that the seat of the initial malarial infection is in the spleen. The capillaries also contain numerous pigmented leukocytes and macrophages.

The *liver* in the tertian infections did not differ in appearance from that of the normal organ, but upon section, the capillaries showed within them a few pigmented leukocytes, some containing what appeared to be degenerated malarial organisms. No infected red cells were observed.

In the æstivo-autumnal infections the pathological lesions were the same and the life-cycle of the parasite could be traced from the earliest hyaline organism to the segmenting bodies, but no crescents could be demonstrated. The only explanation of this fact is that the parasites had not advanced as yet to the stage in which crescent formation was possible.

The pathology of latent malarial infections can be summed up by saying that before demonstrable clinical symptoms of malaria are present the malarial plasmodia are undergoing their human life-cycle within the spleen and can be demonstrated in this organ after death. The changes produced are the same in character as occur in acute infections, but of course not so marked in extent.

It is obvious that puncture of the spleen as a diagnostic measure in these cases would result in the discovery of the malarial infection.

SYMPTOMS.

Incubation.—The incubation period of malaria has received a great deal of attention, but at the present time there is considerable confusion regarding it. Marchiafava and Bignami have contributed a valuable study of this subject, in which they found that the incubation period, from the time the patient was bitten by the mosquitoes until the first symptoms appeared, varied from nine to ten days. Osler states that in the irregular fevers the incubation period varies from three to five days, while in the regular it varies from ten to twelve. From inoculation experiments, Bastianelli and Bignami found that in æstivo-autumnal infections the maximum period of infection was five days, the minimum two, and the mean three days. Mannaberg in seven cases found the period of incubation to vary from three to fourteen days, while Marchiafava and Bignami found the maximum to be fourteen days and the minimum two. As regards the data obtained from inoculation experiments, it may be stated that the disease was inoculated in an unnatural manner, and that for this reason the data may be unreliable. In inoculation of blood containing only the forms of the parasite belonging to the human cycle it is reasonable to suppose that the period of incubation will be shorter than is the case when the mosquito transmits the *sporozoites* to man, and this has been proven experimentally, for Marchiafava and Bignami have found that in an individual stung by the mosquito which had sucked blood con-

taining crescents, æstivo-autumnal fever developed in from nine to twelve days, whereas in the inoculation experiments of all the authorities quoted the mean was six days. But though the period of incubation of these fevers is doubtless in the majority of cases from nine to twelve days, numerous instances do occur which show a much longer period of incubation, sometimes weeks or months. Sternberg quotes the instance of certain sailors who were infected while their ship lay for two days in port and developed the disease, one after forty-eight, and one after one hundred and four days after leaving the port. The period of incubation may be very much prolonged, and in authentic instances personally observed the first symptoms of malaria did not appear until from seven to ten months after exposure. These were in the person of officers and enlisted men of the army serving in a tropical climate, exposed to æstivo-autumnal fever and who immediately afterward were stationed in localities in which there were no *Anopheles* mosquitoes and no endemic foci of malaria. As Osler says, "A patient may dwell for years in an infected region without having paroxysms, or indeed fever of any sort, and he may then come under observation for the first time with anæmia and a greatly enlarged spleen and liver."

The explanation of these long periods of incubation is made clear by the theory advanced by Thayer; *i. e.*, that the parasites multiply and undergo their life-cycle, but in such small numbers that they give rise to no observable clinical signs.

Although many individuals in malarial localities do not present symptoms of malaria for long periods of time, it is without doubt true that in the great majority of instances an individual exposed to infection will acquire the disease in from three weeks to two months. This was well illustrated in the case of our soldiers in Cuba, almost ninety-five per cent. of whom gave a history of being there from two to six weeks before the onset of malarial fever. One month was the most common period given by the men as intervening between landing in Cuba and the first chill.

The length of the period of incubation will vary, of course, with the amount of the infecting agent, the physical condition of the infected individual and his surroundings as regards exposure, heat and cold, insufficient nourishment, etc.

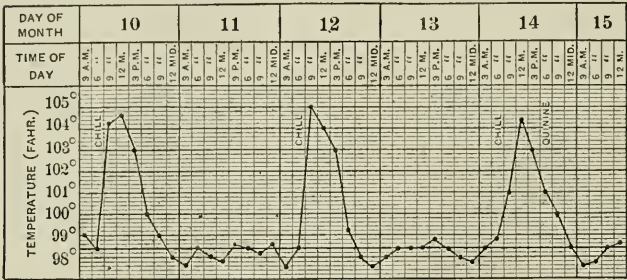
Classification.—It is extremely difficult to classify the malarial fevers from a clinical standpoint. A division into intermittent, remittent and continuous fevers, while useful, is at best but a rough classification which does not signify disease entities and which is confusing in many ways. It may be stated that any malarial fever may be intermittent, remittent or continuous. For instance, while a single tertian infection is undoubtedly intermittent, we can conceive of a tertian infection in which several generations of parasites may mature at various times, giving rise to a remittent or even continuous temperature curve. The same is true of quartan, and especially of the æstivo-autumnal infections. It is also true that infection with one generation of any of the malarial plasmodia will always result in a typical intermittent fever. In other words, *all* malarial infections are intermittent in character and only become remittent or continuous when more than one generation of the plasmodium matures at different intervals of time. While the term remittent malaria is generally applied to infections due to the æstivo-autumnal parasites, the name is a misnomer,

as the æstivo-autumnal infections are as truly intermittent as are the tertian and quartan. For this reason it seems better, in considering the symptomatology to classify the malarial fevers from an etiological standpoint; *i. e.*, tertian, quartan and æstivo-autumnal.

Symptoms of Tertian Malaria.—The paroxysms of fever in tertian malaria occur every forty-eight hours and are due to the segmentation of the tertian malarial plasmodium. The time of the paroxysm can be accurately judged by the stage of growth of the organism as seen in the peripheral blood. The onset of the paroxysm always occurs during the segmentation of the organism, and quotidian paroxysms are caused by double infections with the tertian parasite.

This, the most common and mildest form of malarial fever, occurs both in tropical and temperate climates, and when uncomplicated, presents a typical temperature curve, showing in single infections a rise of temperature every second day, while infections with numerous groups of

FIG. 26.



Tertian Malarial Fever.

tertian organisms may give rise to a remittent or sub-continued fever. In cases which present quotidian paroxysms it is often possible to destroy one group of parasites by small doses of quinine, and, when this is done, the regular tertian paroxysm will reappear.

The paroxysm, when typical, is divided into three stages, chill, fever, and sweating. The *prodromal* symptoms are generally malaise, loss of appetite and more or less dull headache. After these symptoms have persisted for a few days the patient is seized with a severe chill, but although he feels extremely cold the temperature continues to rise and at the acme of the chill has reached 103°, 104°, or even 106° F. The chill is immediately followed by a pronounced sense of heat, and in a short period of time the patient will complain as bitterly of this as he previously had of the cold. During the stage of fever, delirium is often present, accompanied by severe headache. During the onset of the chill, nausea and vomiting are common, but they do not persist, as a rule, during the stage of fever. After the fever has lasted for a few hours, it rapidly declines to normal, accompanied by very severe sweating, the entire skin being bedewed with moisture, often so pronounced that the bed-clothing is saturated.

The Cold Stage.—As has been mentioned, there are generally some prodromal symptoms of the approaching malarial chill, as evidenced by yawning, a general sense of discomfort, headache, and often nausea and vomiting. The feeling of cold usually commences at the feet and gradually progresses upward, although very often the first chilly sensations are felt along the spine. In this form of infection the chill is severe, the patient shaking very vigorously, but, it is not so severe as in the quartan infections. In certain mild cases the chill may be absent, the patient complaining only of chilly sensations. The facial expression of the patient during the chill is one of cyanosis, the lips being blue and the skin bluish-red in color. The extremities are cyanotic and the skin presents the well-known condition characterized as “goose flesh.” The pulse is rapid, generally rather diminished in volume and often irregular. Headache is very often intense. During the chill the temperature rises very rapidly, reaching 104° F. or more, but careful examination will demonstrate that it has begun to rise before the onset of the chill. The urine is increased in quantity and lowered in specific gravity. The duration of this stage varies from one quarter of an hour to two hours in the most severe cases.

The Hot Stage.—At the commencement of the hot stage the patient complains of flushings of heat, rapidly succeeded by cold sensations. Soon the sensations of cold are entirely lost and the patient complains bitterly of the intense heat occasioned by this high temperature. The facial appearance is that of congestion, the conjunctiva being injected and the skin red, while the entire surface of the body is reddened and the congestion is especially marked in the hands. The pulse is full, bounding and often dicrotic. The respirations are often rapid and hurried, and there may be more or less cough, denoting congestion of the lungs. The headache increases and may become very intense and of a throbbing character. Epistaxis occurs in a small proportion of the cases. In the milder tertians there are no nervous symptoms present beyond a severe headache, but in the severe cases there may be marked delirium or a drowsy condition merging into a semicoma. This condition is almost always present in those rare cases of tertian infection which become pernicious. The chief symptoms complained of by the patient during the hot stage are the severe headache and the intense heat. The temperature may reach its extreme height during this stage but very often the height of the fever is reached at the end of the cold stage. It is not uncommon during the hot stage to observe cutaneous eruptions. Herpes is very frequently seen, especially on the lips, and urticaria and a general erythema not infrequently occur. These eruptions sometimes lead to a suspicion of some eruptive disease being the cause of the chill. Herpes of the penis may occur during the hot stage of the paroxysm. The duration of this stage varies somewhat, but is generally from four to six hours.

The Sweating Stage.—As the fever begins to decline, it will be noticed that the perspiration appears first on the forehead and face, and the patient at once begins to feel better, the decrease in the unpleasant symptoms being proportionate to the severity of the sweating. Commencing, as has been said, on the face, the perspiration rapidly involves the entire body and is often so severe that water may be seen trickling from the skin of the arms, thighs, and legs. The sweating stage lasts, as a rule from two to three hours, at the end of which time the temperature has

Symptoms of *Æstivo-Autumnal Infections.*—Clinically, all *æstivo-autumnal* infections should be classed as severe infections, in contradistinction to the quartan and tertian infections, which are usually considered as mild infections. It should be thoroughly understood, however, that a quartan or tertian infection may become pernicious, although such instances are rare. The old idea that there is a malarial parasite peculiar to the pernicious infections is no longer tenable, for it is now recognized that any of the malarial parasites may induce pernicious symptoms, and that the parasites accompanying such infections do not differ in any respect from those accompanying the mildest infections.

The *æstivo-autumnal* infections occur in temperate regions most frequently during the months of July, August, September, and October, but in the tropics they persist throughout the year, and are not characterized by any marked seasonal prevalence.

As has been stated, the writer believes that these infections are caused by two distinct varieties of the *æstivo-autumnal* parasite, one completing its cycle of development in the human body in twenty-four hours, and the other in forty-eight hours. Either of these parasites is capable of causing pernicious infections, but personal observations suggest that the tertian *æstivo-autumnal* parasite is the one most commonly concerned. From personal observations embracing nearly 2,000 cases of *æstivo-autumnal* fever in which the parasites were demonstrated in the blood, 75 per cent. were due to the tertian *æstivo-autumnal* variety.

The *æstivo-autumnal* infections have long been distinguished by the term remittent, it being supposed that in these infections the temperature curve, instead of presenting the marked intermittency observed in tertian and quartan infections, was remittent or irregular in character. This is, however, not always correct, for these infections, when uncomplicated or uninfluenced in any way by treatment, may be as truly intermittent as are the tertian and quartan infections. It is undeniable, however, that remittency and irregularities in the temperature curve are more common in the *æstivo-autumnal* infections, but too much stress should not be laid upon this point in diagnosis.

Symptoms of Tertian *Æstivo-Autumnal* Fever.—Patients suffering from this variety of malarial infection will present, as a rule, the following symptoms:

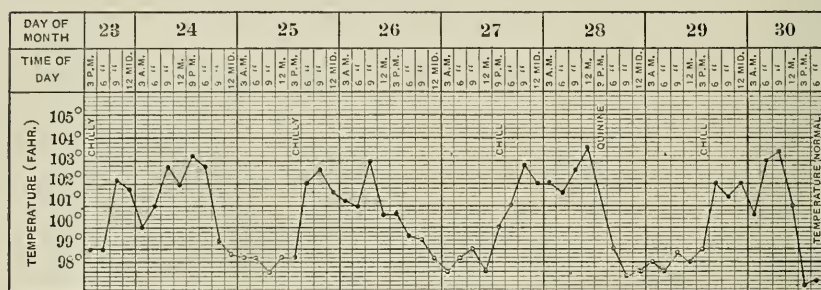
Prodromal.—The prodromal symptoms are loss of appetite, slight headache, evanescent pains in the back and legs, nervousness, increased urination, and a general feeling of malaise. As in the tertian and quartan infections, three stages may be distinguished.

The Cold Stage.—This commences with yawning and the patient complains of headache, slight nausea, perhaps accompanied with vomiting, and often intense nervousness. In a majority of cases there are no distinct chills, but the patient complains of creeping sensations along the spinal column and slight flushings of cold especially noticeable along the posterior portion of the buttocks and thighs. At the same time the headache increases and there is generally profound mental depression. The mucous membranes are cyanosed and the extremities cold. There is severe pain in the legs and back, greatest, as a rule, in the lumbar region. The pulse is generally weak and increased in frequency and may be very irregular. The respirations are rapid and rather shallow. During this

stage the temperature is elevated and may reach 103° F. or more. This portion of the attack does not last over half an hour in a majority of the cases.

Hot Stage.—The patient next experiences a sense of heat which comes first as localized flushings, but soon becomes general. The facial expression is that common to fever, the eyes being suffused and brilliant, the face red, and the skin hot and dry. Headache is intense and there is present either great mental depression or nervous excitement. The pain in the back and limbs is often agonizing in character, and in some instances

FIG. 28.



Tertian æstivo-autumnal fever.

there is severe pain over the abdomen. The temperature is elevated and the curve very characteristic. Nausea and vomiting are often present, vomiting being sometimes very severe. The urine is increased in quantity and is generally albuminous. Diarrhœa is a common complication. The pulse is rapid and dicrotic in character, the respiration rapid, and there may be severe dyspnœa. This stage lasts for several hours, often from sixteen to eighteen or twenty, and is succeeded by a stage of remission. During this time the symptoms gradually decline in severity and finally disappear, the temperature returns to normal, generally going a degree or degree and a half below normal. A slight sweating occurs but this is not nearly so marked as in the tertian and quartan paroxysms. The intermission may last only two or three hours when another paroxysm ensues. As a rule, attacks of this fever occur toward evening, extend throughout the next day, and subside during the first hours of the third day, the entire paroxysm thus lasting thirty-six hours or more and occurring every forty-eight hours.

While the symptoms described are often more severe than they are in the tertian and quartan infections, there is nothing diagnostic about them except the temperature curve. In uncomplicated cases the behavior of the temperature is absolutely characteristic, and the temperature curve is one that is not met with in any other disease. This peculiarity of tertian æstivo-autumnal infection was first pointed out by Marchiafava and Bignami, and the writer has confirmed their observations in every uncomplicated case of such infection. At the onset of the fever the temperature rises suddenly to 103° or 104° F. Following the sudden rise

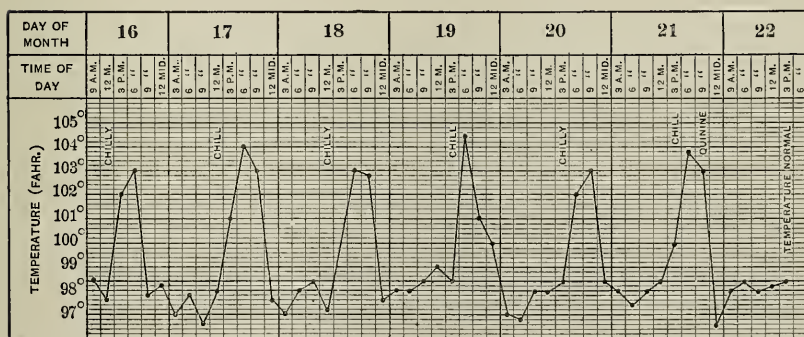
there occur slight oscillations which cover several hours, during which time the temperature falls from one-half to one degree. This period of oscillation is followed by a distinct fall or pseudo-crisis, the temperature dropping from one and one-half to two, or even three degrees. This fall of temperature is often considered by the physician as the true crisis of the paroxysm. On the contrary, however, the fever again rises to a point higher than before attained and then falls rapidly. This is the true crisis, as the temperature goes considerably below normal. This peculiar temperature curve can be divided into five stages: (1) the initial rise; (2) the period of slight remissions; (3) the pseudo-crisis; (4) the precritical stage; (5) the true crisis.

Another point of value in diagnosis between this type of fever and the mild tertian and quartan types is the length of time during which the fever lasts. This varies, but generally the temperature remains elevated over twenty-four hours, and often from thirty-eight to forty; in other words, the paroxysm really covers two days, while the period of intermission is very short.

While this peculiar temperature curve will be observed in a very large proportion of cases of tertian æstivo-autumnal malaria, there may be many deviations from it due to several factors, among the most important being improper medication; double infections, or infection with more than one variety of malarial parasite; anticipation of the attacks or retardation, which are especially common in the pernicious forms; and slight elevations of the temperature occurring between the paroxysms. The ordinary temperature chart which shows only the morning and evening temperature is worse than useless as a guide in studying this form of fever. The temperature should be taken at least every four hours and better every three.

Symptoms of Quotidian Æstivo-Autumnal Infections.—The quotidian infection, which depends for its etiology upon the quotidian form

FIG. 29.



Quotidian æstivo-autumnal fever.

of the æstivo-autumnal parasite, varies but slightly in its symptomatology from the tertian, except that the paroxysms occur every twenty-four hours. As a rule, in the quotidian cases the chilly sensations are more severe and

there is often a distinct chill. Sweating is also more pronounced but is not so marked as in the simple tertian and quartan fevers. The temperature curve is entirely different. It consists in the abrupt rise of the temperature to 103° F. or more, succeeded by as abrupt a fall. The attack lasts as a rule only about eight or ten hours. The temperature curve seldom remains regular for long at a time, for the attacks tend to run into one another, thus giving rise to a continuous fever. This is especially true of those cases of a pernicious type. The temperature curve in the quotidian form is not characteristic as it resembles very closely that of double tertian infection, and we must therefore depend upon the microscope in making our diagnosis. There is no greater proof of the value of a microscopic examination of the blood than is found in the case with which the various forms of malarial fever may be diagnosed and differentiated by it, and such an examination is often instrumental in saving life.

Pernicious Malarial Infections.—Any one of the malarial plasmodia may give rise to pernicious symptoms, but the vast majority of fatal cases of malarial fever are due to the æstivo-autumnal parasites. The tertian æstivo-autumnal parasite is more often concerned in such infections than is the quotidian, but it should be remembered that tertian infections are very much more numerous than are the quotidian. It is very important in treating cases of æstivo-autumnal malaria to remember that there is always an element of danger in that they may at any time develop pernicious symptoms which may cause the death of the patient, and it should be distinctly understood that the pernicious forms of malaria depend for their etiology upon the same organisms as do the mildest forms.

The great majority of pernicious attacks of malaria occur in northern latitudes in the summer and autumn and are rare, while in the tropics they occur throughout the year and are very common. The most pernicious attacks occur in patients who have suffered repeatedly from malarial paroxysms which have not been properly treated, and the pernicious symptoms often develop during such a paroxysm. The causes of the pernicious symptoms are not very clearly understood. Bastianelli and Bignami considered that the chief causes for the development of the pernicious symptoms rest in the localization of the parasites in the brain or in other important organs, and also in the number of parasites present. While these reasons undoubtedly have much to do with the development of pernicious symptoms, it is probable that the amount of toxins secreted by the parasites have much to do with the development of these symptoms, as well as the physical condition of the infected individual and his surroundings as regards climate, food, hardships, etc.

The pernicious forms of malaria may be classified in two ways; *i. e.*, from the character of the temperature curve, and from the most prominent symptoms which are present. Under the first classification we may have *tertian*, *quartan*, *remittent* or *larval* pernicious malaria. Under the second classification we may have *comatose*, *delirious*, *tetanic*, *eclamptic*, *hemiplegic*, *dysenteric*, *choleraic*, *algid*, *cardialgic*, *hemorrhagic*, *pneumonic* and *bilious* pernicious malaria fevers. Only a few of the most common varieties will be described and it should be remembered that these are not disease entities, but only take their name from the clinical symptoms which are present.

The Comatose Form.—This is the most frequent form of pernicious malarial fever and occurs in two ways, either as a sudden attack of coma or a gradually developing comatose condition during a paroxysm of fever. The sudden development of coma is rare and, unless at once recognized and treated, invariably fatal. In this form the patient, who may have suffered from repeated attacks of malaria and who has not felt well for some time, is suddenly stricken with profound coma, falls to the ground and, in the fatal cases, does not again regain consciousness. This form is apt to be mistaken for apoplexy. The face is suffused, the pupils contracted, the pulse at first full and bounding, later soft, rapid and thready, the respirations hurried and sometimes stertorous. The temperature is irregular, seldom reaching 103° F., and is often subnormal. Death generally occurs within two days. The most common form of comatose malaria is that in which coma develops more or less gradually during an attack of the fever. The symptomatology of the attack is the same as in the ordinary paroxysm, but the nervous symptoms such as restlessness and delirium may be more marked. As a rule the patient is restless and mentally depressed. Following this there develops a tendency to somnolence, which deepens into stupor and finally coma. Unconsciousness is complete, the patient lying perfectly quiet, or there may be restless movements of the arms and legs. The skin is often somewhat icteric in hue, and hot and dry; the pupils are generally equally contracted but may be unequal or equally dilated. The icteric hue, which is often present in the conjunctive, has led to a diagnosis of yellow fever in infected regions. The face may be cyanotic but in old infections it is generally pale. Slight spasms of the muscles of the face are not infrequent. The tongue is tremulous, dry, and thickly coated, and slight hemorrhages into the skin are sometimes observed. There may be hemiplegia present or total paralysis. The respirations are slow and quiet, but may be irregular, rapid and stertorous. The pulse is generally slow and full and incompressible at first, but becomes rapid and weak as the paroxysm progresses. The feces and urine are passed involuntarily, and retention of urine may occur. In cases having a fatal termination the pulse becomes thready, rapid and intermittent; the respirations irregular, labored or shallow; the skin pale and bedewed with cold perspiration, and death occurs by collapse. In cases which recover, the temperature falls, accompanied by perspiration, the consciousness is slowly regained, but in many of these cases the improvement is only apparent and the patient relapses in the course of a few hours into a second paroxysm, and perhaps into a third, which usually results fatally. Between the paroxysms the mental condition is one of torpor or great mental depression accompanied by severe headache. The duration of the coma is variable, lasting from a few hours to three or four days, but it generally does not persist longer than twenty-four to twenty-six hours.

As regards the course of the temperature in this form of pernicious malaria, it may be stated that it is irregular. Some cases present high temperature throughout, between 103° and 104° F., while in others the temperature may remain slightly above normal, or even below normal. In fatal cases the fever if present, declines, as a rule, some hours before death, but it may ascend. Manson cites temperatures of 101° and 112° F. In a fatal case observed by the writer the temperature never went above

101° F. until a few hours before death, when it rose to 103°, the entire attack lasting six days. In this case the disease was not recognized by the attending physician until a few hours before death, when a blood examination was asked for, and large numbers of quotidian æstivo-autumnal parasites were found.

Besides the comatose form of pernicious malaria there are other cerebral forms, among which may be mentioned the *delirious* form in which the patient has hallucinations, followed by violent excitement; the *eclamptic* form, which is common in children, in which the symptoms are similar to those of cerebro-spinal meningitis, there being vomiting, fever, headache, pain in the back of the neck, convulsions, and coma; the *hemiplegic* form characterized by hemiplegia; and the *amaurotic* form, in which, after the comatose symptoms have subsided, complete blindness may result.

The Algid Form.—In certain regions of the Southern and Middle States, as well as in other localities, there occur pernicious forms of malaria known as algid forms. The symptoms develop after one or more paroxysms, or they may be the primary symptoms. The characteristic condition is one of profound collapse attended by profuse perspiration, the temperature at the same time being more or less elevated, although in many cases the temperature is subnormal. Patients suffering from this form of malarial infection present a characteristic countenance, the cheeks being drawn and pinched, the eyes sunken, the nostrils dilated and the skin bedewed with perspiration. The entire body is cold and the skin cyanotic and bathed with cold sweat. The lips and finger nails are intensely cyanotic. The tongue is tremulous, dry, and coated with a dirty white fur. The pulse is rapid, thready, and easily compressible, and generally more or less intermittent; the heart sounds are muffled and the second sound sometimes inaudible, and as death approaches the pulse becomes imperceptible; the respirations are irregular, superficial in character, and labored; the muscular weakness is extreme, while the mental condition of the patient is one of apathy to his surroundings and indifference as to his condition. These symptoms rarely last over a few hours, death generally resulting. This is one of the most pernicious types of malarial infection and one which is most resistant to treatment. Such cases have been described by Laveran, Thayer, Marchiafava, Bignami, Osler and Sternberg. In one case observed by the writer in the person of a volunteer soldier who contracted æstivo-autumnal fever in Cuba, algid symptoms developed and death occurred after six hours, despite all therapeutic aid. He had suffered previously from several paroxysms and his blood showed large numbers of æstivo-autumnal parasites.

The Choleraic Form.—In certain cases of pernicious æstivo-autumnal malaria, the patient presents symptoms which very closely simulate those of cholera. As has been mentioned, diarrhœa is by no means an infrequent symptom in attacks of æstivo-autumnal fever, but in these cases choleraic symptoms develop, the stools suddenly becoming watery, very profuse and numerous. The diarrhœa leads to profound collapse accompanied by the usual symptoms. Death is a common result in untreated cases, but where therapeutic measures are applied promptly, recovery occurs in the majority of cases. The temperature is generally

elevated in this form. The great importance of this variety of æstivo-autumnal fever consists in the liability with which it may be mistaken for cholera in countries in which epidemics of cholera are common. Microscopic examination of the blood is the only absolutely correct method of arriving at a diagnosis in such cases.

Closely allied to the choleraic form, so far as symptoms pointing to the abdomen are concerned, is the *gastralgie* form which has been described by Laveran, Colin, and Haspel. Prominent symptoms are agonizing pain in the epigastrium, the vomiting of matter tinged with blood, while a diarrhœa severe in character may also occur at the same time. This form is interesting from a surgical standpoint, as a diagnosis of appendicitis may be made.

The Dysenteric Form.—A considerable proportion of patients suffering from æstivo-autumnal infection present symptoms of dysentery, consisting in frequent mucoid and bloody stools, tenesmus, colicky pain in the abdomen, progressive emaciation, etc. At the Army General Hospital, Presidio of San Francisco, California, a very large proportion of æstivo-autumnal patients coming from the Philippine Islands presented dysenteric symptoms. In fact, sixty-five per cent. of the cases of unrecognized malarial fever observed there were diagnosed either as chronic diarrhœa or dysentery. This proves how commonly dysenteric symptoms in the tropics are due to malarial infection, and probably a certain proportion of cases diagnosed as dysentery in tropical regions are in reality the dysenteric form of malarial infection. The proper administration of quinine in these cases has always resulted in the disappearance of the symptoms, thus proving their malarial nature.

The Bilious Form.—Certain cases of malarial infection present a symptom complex in which jaundice and the vomiting of bile-stained fluid are most prominent. These cases have long been known under the term of bilious remittent fever. The attack is generally characterized in the beginning by well-marked malarial paroxysms, but the temperature becomes more or less remittent or continuous. Marked jaundice appears and severe vomiting is present, the matter vomited being greatly bile-stained. Epistaxis is rather common, and hæmatemesis often occurs. Delirium may be present or there may be a condition of semi-coma, or even coma. The patient often complains of severe pain in the epigastrium and hiccough is one of the most common symptoms. The temperature curve in well-marked cases is generally remittent or almost continuous, somewhat resembling that of typhoid fever. If untreated, this form of the disease is almost invariably fatal, but if the proper therapeutic measures are applied recovery is generally the result.

The Irregular and Remittent Forms.—As has been stated, any of the malarial infections may become irregular or remittent in character as regards the temperature, but the æstivo-autumnal infections are especially prone to present peculiar irregularities in the fever, which in many cases are very confusing. A malarial fever may become continuous, irregular or remittent in various ways, the principal of which are the anticipation or retardation of the paroxysm, infection with one or more groups of parasites, and insufficient treatment by quinine. In these infections it is very seldom possible to demonstrate the complete life-cycle of the parasite in the blood, but in those cases which are caused by mixed infection

very rare instances the parasites may be very resistant to quinine and persist for eight or ten days.

Spontaneous recovery, which has been mentioned, is often observed in the mild tertian and quartan infections and rarely in the æstivo-autumnal infections. The chief causes leading to spontaneous recovery in malaria are:

1. Production and excretion of certain substances bactericidal and antitoxic in nature, by certain leukocytes, especially the eosinophiles, which lead to the death of the malarial plasmodia.

2. Disintegration of the leukocytes and the liberation of certain antitoxic and bactericidal substances having a similar action.

3. Phagocytosis; *i. e.*, the engulfing and digestion of the plasmodia.

It is probable that all of these processes occur simultaneously and aid in the destruction of the infection.

Combined Infections.—Any of the varieties of malarial plasmodia may occur together, thus causing what is known as a combined infection. In such infections the temperature chart is apt to be irregular or remittent, but very often one type of parasite may so predominate in numbers that it will give to the infection the characteristic symptoms caused by the particular organism concerned; thus we may have a combined infection with æstivo-autumnal and tertian parasites in which the æstivo-autumnal parasites are so much more numerous than the tertian that the case will present the symptoms of an æstivo-autumnal infection. As would be expected, some very peculiar temperature charts are presented in these combined infections, and the symptoms are often so anomalous that a diagnosis of malaria cannot be made without the aid of the microscope.

Latent and Masked Infections.—In previous communications¹ the writer has called attention to the importance of the occurrence of latent and masked malarial infections, especially in individuals who have resided in malarious localities. A latent malarial infection may be defined as one in which parasites can be demonstrated in the blood but in which there are no symptoms which would lead a clinician to suspect malaria, while a masked infection is one in which the symptoms are obscured by those of some accompanying disease, or in which they are atypical in character. At the U. S. Army General Hospital in San Francisco, California, out of 1,267 cases of malaria in which the parasites were demonstrated in the blood, 395, or 25 per cent., have shown either latent or masked infections. The æstivo-autumnal infections comprised 275 of the cases, thus showing that the æstivo-autumnal parasite is concerned most often in latent and masked malaria. Examinations of the blood in such cases have shown the parasites in all stages of development, but always in small numbers. Of the 395 cases, 277 were latent infections, or infections in which the malarial parasites could be demonstrated in the blood but which presented no clinical symptoms, while 118 were masked infections, most of them being in patients suffering from other diseases which masked the malarial symptoms. Of the masked infections, chronic dysentery, chronic diarrhœa, pulmonary tuberculosis, and amœbic dysentery were the diseases which most often masked the malarial infection. Lobar pneumonia was simulated very closely in three cases by the malarial infection, and a

¹ *Medical Record*, Feb. 15, 1902, also *American Medicine*, Oct. 21, 1904.

diagnosis of this disease was made previous to an examination of the blood.

The pathology of certain fatal cases of latent and masked malarial infection demonstrates that the malarial parasite may undergo its complete life-cycle in the spleen without producing any symptoms of the disease.

The remarkable percentage of latent and masked infections, as shown in the cases studied at this hospital, proves the great importance of a routine examination of the blood in all patients coming from malarious localities. It is obvious that recognition of such infection is of the greatest importance, as in the latent infections we are thus able to cure the disease before any annoying symptoms are present, and in the masked cases we are able to remove the malarial element which may be of the greatest importance as regards the recovery of the patient. Not only is this so, but an examination of the blood in these cases will often prove of service, not only to the physician, but also to the surgeon, as certain malarial infections simulate very closely surgical conditions. The following case is of especial interest, as it demonstrates how closely malarial infection may simulate appendicitis.

The patient was an officer of the U. S. Army who was transferred to the Army General Hospital with a diagnosis of suspected appendicitis, transfer being made with a view to operation if the diagnosis was verified. He gave a history of having intermittent attacks of malaria in the Philippines which did not necessitate admission to sick report. He had not been feeling well for some time, but on the day before admission to the hospital he had an attack of pain in the region of the ascending colon. Upon admission he complained of pain in this region, at times very severe; his tongue was coated; bowels regular; and his pulse and temperature about normal. A blood count was made and a slight leukocytosis was found. Physical examination showed no rigidity of the muscular wall, but he complained of pain in the right iliac region on pressure, and after careful examination, operation the next morning was determined upon. That evening he had a slight chill and his temperature rose to 104° F. An examination of the blood was made and numerous hyaline forms of the tertian æstivo-autumnal parasite were found. Quinine was promptly administered, which resulted in a prompt fall of temperature, and continued administrations of it in a complete cure. In this case an operation would undoubtedly have been performed in the morning for a condition which was essentially malarial in character. Microscopic examination of the blood in these cases is our only means of diagnosing the disease.

Complications and Sequelæ.—The malarial fevers, like other disease processes, are apt to be complicated by, or associated with, other diseases, and are also apt to be followed by certain grave sequelæ. While this is so, the conditions complicating malarial infection should not be confused with the infection itself; in other words, a typhoid fever complicating malaria should not be considered as being due to malarial infection; nor is a pneumonia which may complicate such infections, due to the malarial parasites. Boudin advocated the theory that the complications were due to malarial poison, but in the light of our present knowledge this theory is entirely untenable. Of the many diseases which may complicate the various forms of malaria, and especially the æstivo-autumnal

infections (for these infections, being more severe in character than the tertian or quartan, are more apt to be accompanied by complications), the following may be mentioned:

Of the diseases of the *nervous* system acute mania, severe hysteria, paraplegia, hemiplegia and meningitis may be noted.

The most serious disease of the *respiratory* system complicating malarial infections is lobar and lobular pneumonia. For a long time pneumonia complicating these fevers was held to be due to the malarial plasmodia, and while this is true in a very small number of cases, it should be remembered that true lobar or lobular pneumonia may occur coincidently with any of the malarial fevers. Pneumonia may complicate the malarial infection at any time, and may develop suddenly or insidiously. The course of the disease is similar to that in a patient in whom no malarial infection is present, but the prognosis in pneumonias complicating the æstivo-autumnal infections is very grave, Ascoli placing the mortality as high as 60 to 78 per cent. The pneumonic symptoms may mask the malaria, or *vice versa*. Among the other respiratory complications may be mentioned pneumonic septicæmia and empyema. Acute bronchitis is very common in all varieties of malarial infection and in the æstivo-autumnal infections is observed in about 40 per cent. of the cases. Tuberculosis very often occurs in conjunction with malarial infections, and often the symptoms of the disease mask those of malaria. Pleurisy is somewhat rare.

Diseases of the *circulatory* system not infrequently complicate malarial fevers. As would be expected, many cases of malaria present organic disease of the heart and in such cases the prognosis is often grave. Acute endocarditis is a rare complication, while functional disorders of the heart are very common.

The most common disease of the *genito-urinary* system complicating malaria is nephritis. Some form of nephritis occurred in at least 4 per cent. of æstivo-autumnal infections and in about $\frac{1}{2}$ per cent. of tertian infections personally observed. It is more frequently a sequel of malaria than a complication. Orchitis and epididymitis very commonly occur as complications, but a history of gonorrhœa can usually be obtained. It is doubtful if true malarial orchitis ever occurs.

The most frequent and important disease of the *gastro-intestinal* tract complicating the malarial fevers is dysentery or some form of enteritis. Dysentery is especially frequent in patients returning from regions where both malaria and dysentery are endemic. Sixty-five per cent. of the patients with malarial parasites in the blood observed at the Army General Hospital, Presidio of San Francisco, suffered at some time from acute or chronic dysentery. Of these over 25 per cent. were suffering from amœbic dysentery. Dysentery complicating malaria is very apt to run an aggravated course, and the prognosis is much worse than where it occurs alone. Frequently the malarial forms are masked by the symptoms of dysentery.

The administration of quinine in cases complicated by dysentery has always resulted in the removal of the malarial infection and the improvement of the dysenteric condition. In a certain proportion of patients suffering from dysentery, the disease is probably due to the localization of the malarial parasites within the capillaries of the intestines, for in no

other way can we explain the rapid recovery of many such patients after the administration of quinine.

Typhoid fever occasionally occurs in conjunction with the malarial fevers. In nearly 5,000 cases of malaria personally observed the complication of the disease with typhoid has only occurred 8 times. Of these 8 cases, 5 were combined infections of typhoid and æstivo-autumnal malaria, 1 a combined infection with tertian malaria, and 1 with quartan. The latter case, which has been reported,¹ is rare, in that the quartan parasite was demonstrated in the blood in combination with typhoid. As a rule, the malarial attacks occur during convalescence from typhoid but may occur during any stage of the disease. Where malaria is complicated by typhoid, or even *vice versa*, the symptoms do not vary markedly from those occurring in a single infection. The subject of combined infections of typhoid and malaria has been very fully investigated by Lyon,² who has collected all the published cases, which, at the time the classification was completed, numbered 29 in all. Undoubtedly, this is far from being the actual number of such combined infections, as Lyon considered only as such infections cases in which the parasites of malaria were demonstrated in the blood at the same time that the Widal test was present.

The discovery of such combined infections is of the greatest importance, as the malarial element in the case can be easily removed by the proper administration of quinine, and thus a source of injury to the patient eliminated.

Among other complications may be mentioned erysipelas, acute rheumatism, sciatica, various skin eruptions and variola.

Sequelæ.—The toxins elaborated during the development of the malarial plasmodia may give rise to certain conditions which develop coincident with or after the malarial infection itself has ceased, and these must be regarded as sequelæ of the disease. Among the most common are those occurring in the *nervous* system, the *genito-urinary* system, the *glandular* system, and the *blood*.

The most numerous complications occur in the nervous system, due to the blocking of the capillaries of the cortex of the brain by the malarial parasites and their products, or to the effect of certain toxins liberated by them. Local paralysis frequently occurs, due undoubtedly to the blocking of the capillaries of certain cortical regions, but these are generally evanescent in character. Various psychical disturbances are common and the memory is often defective after repeated malarial attacks. Melancholia, delusional insanity and mania may follow severe attacks of æstivo-autumnal malaria, and especially common is a condition of melancholia. Mania, melancholia and delusional insanity have been observed in soldiers returning from the tropics which were undoubtedly sequelæ of severe and repeated attacks of æstivo-autumnal malaria. Multiple neuritis rarely occurs. One of the most common sequelæ is neuralgia, but it should be remembered that many so-called malarial neuralgias have in reality no connection whatever with malarial infection.

¹ *Philadelphia Medical Journal*, June 17, 1899

² *The Johns Hopkins Hospital Reports*, Vol. VIII, 1900.

Among diseases of the genito-urinary system, albuminuria is of frequent occurrence during acute attacks of malaria and oftentimes persists for some time after the cessation of such attacks. Thayer and Hewetson found albuminuria in over 50 per cent. of their cases. Thayer found that it was most frequent in æstivo-autumnal infections, occurring in 58.3 per cent. of these infections, in contrast to 38.6 per cent. of tertian and quartan infections. Rem-Pici has contributed most extensively to our knowledge of the albuminurias occurring during and after malarial infections. From personal experience, albuminuria apparently occurs in about 50 per cent. of cases of æstivo-autumnal and in about 30 to 35 per cent. of cases of tertian and quartan malaria.

Both acute and chronic nephritis may occur as sequelæ of the malarial fevers. Kelsch and Keiner have contributed valuable data regarding the symptomatology and pathology of nephritis occurring after malarial infections. It may be stated that all forms may occur, the most common being acute glomerular and chronic parenchymatous and interstitial nephritis. Personal observations suggest that nephritis occurs in at least 3 per cent. of all cases of æstivo-autumnal infections, the most common form being chronic parenchymatous. It is rare in tertian and quartan infections, but is always found in fatal cases.

Polyuria is a frequent sequela of the malarial fevers, especially the æstivo-autumnal variety, but as a rule the condition is transient, although it may be persistent. Glycosuria is a rare sequela of the malarial infections.

Among the sequelæ occurring in the glandular system may be mentioned hypertrophy of the liver and rupture of the spleen. After repeated attacks of malaria, a condition which may be termed hypertrophic, malarial hepatitis may develop, the liver becoming greatly enlarged, while the perilobular tissue is increased in amount and the capillaries greatly dilated and congested. The condition does not, as a rule, cause any clinical symptoms. Many authorities have endeavored to prove that continued malarial infection will give rise to cirrhosis of the liver, but when present it is undoubtedly due to some other cause, as cirrhosis of the liver is no more common in malarial than in non-malarial districts.

Rupture of the spleen is a rare sequela of malaria and is generally due to falls or blows, in which the greatly enlarged organ, rendered soft and pliable by the malarial infection, is ruptured. The writer has reported two cases of this character. The symptoms are sharp, lancinating pain in the left side and the usual symptoms of collapse due to hemorrhage. Death may occur in a few moments or after a day or more.

The Blood.—In repeated and severe attacks of æstivo-autumnal malaria there is produced a post-malarial anæmia which may be very severe and persistent. In tertian and quartan infections, after complete recovery the regeneration of the red blood corpuscles is generally rapid, but in the æstivo-autumnal infections the anæmia may persist. Along with the anæmia there is a marked reduction in the hæmoglobin, always in about the same ratio as the red blood corpuscles, while the leukocytes are reduced in number as a whole, but the large mononuclear forms increased.

A pernicious type of anæmia, occurring as a sequela of the æstivo-autumnal infections, have been observed by the writer in 6 cases, all of

which proved fatal. The blood showed no nucleated red cells, the red cells numbering from 490,000 to 590,000 per cubic millimeter. The leukocytes were about normal in number, relatively, but the polymorphonuclear leukocytes were increased. Poikilocytosis was not marked, but there were great differences in the size of the red cells. This form of severe anaemia has been described by Bignami and Bastianelli, and is remarkable in that no nucleated red cells can be demonstrated, due, according to these authors, to the almost complete absence of regenerative power in the blood-forming organs. In certain instances the classical type of pernicious anaemia may occur as a sequela of the malarial infections, especially the æstivo-autumnal variety.

Malarial Cachexia.—In patients who have suffered from repeated attacks of malarial fever which have not been properly treated, there develops a peculiar condition, the most characteristic symptoms of which are a more or less severe anaemia and a greatly enlarged spleen. This so-called malarial cachexia is most frequent in tropical regions in which the æstivo-autumnal infections are endemic, and least frequent in localities in which tertian infections are present. It is especially apt to develop after latent and masked infections which have gone untreated because unrecognized. The anaemia which is present partakes of the character of a secondary anaemia, the red cells being reduced to 2,000,000 or less per cubic millimeter, while there is a marked increase in the large mononuclear leukocytes and a corresponding decrease in the hæmoglobin. The spleen may be enormously enlarged, reaching as low as the crest of the ilium, but as a rule it does not extend more than four to eight cm. below the border of the ribs. It is firm and not painful on palpation.

Patients suffering from malarial cachexia present a peculiar yellowish or grayish hue of the skin, while the mucous membranes are very pale, due to the anaemia. There is a loss of appetite, diarrhoea, dyspnoea, emaciation, and a general condition of nervous exhaustion. The temperature may be normal, but generally shows a slight rise toward evening; it seldom reaches 102° F. The condition is especially frequent in children living in tropical localities.

The long-continued malarial infection renders these patients especially liable to acute infectious diseases and slight injuries are often attended by serious results, such as phlegmonous inflammation or hemorrhage. Marchiafava and Bignami state that it has never been their experience to observe in patients suffering from malarial cachexia, grave infections with many parasites in the blood, but that there are always a few parasites and very little melanæmia. Thus it will be seen that malarial cachexia cannot always be determined by microscopic examination of the blood, as the parasites will not be present in any number except when there are acute symptoms, and even melanæmia may be almost absent.

Diagnosis.—The diagnosis of the malarial fevers from clinical symptoms alone is often difficult and sometimes impossible, especially in the æstivo-autumnal infections, but there are two methods of diagnosis which are all-sufficient and deserving of confidence; *i. e.*, examination of the blood and the therapeutic test by quinine. Of these two methods the examination of the blood is the more valuable, for the therapeutic test by quinine may be misleading, as other fevers may decline under the administration of this drug. The mild tertian and quartan infections, if

uncomplicated, can usually be easily diagnosed by the clinical symptoms alone, but where double infections occur, a diagnosis of malaria is often impossible from a clinical study of the symptoms, and in æstivo-autumnal infections a diagnosis of malaria is generally impossible without an examination of the blood, as the symptoms are often so confusing and atypical that they are of little value.

Examination of the Blood.—In most instances one examination of the blood will be sufficient, but if a negative result is obtained repeated examinations should be made at short intervals. If this is done, almost invariably, even in the most obscure æstivo-autumnal infections, the parasites will be discovered. Cases of malaria of this variety undoubtedly occur in which no parasites can be demonstrated in the peripheral blood, but not when the infection is severe enough to produce symptoms. The symptoms in æstivo-autumnal infections are often so obscure, or even so slight, that malaria is not suspected, and in many cases an examination of the blood will show the presence of the malarial plasmodia before any clinical symptoms sufficiently severe to excite a suspicion that the infection existed. It follows, then, that an examination of the blood in all cases of disease occurring in malarious localities should be adopted as a routine measure.

The blood may be examined either in the fresh state or in stained specimens. The desirability of the examination of the blood in the fresh condition rather than in permanent specimens, which have been hardened and stained, has been advised but since the development of Wright's modification of Romanowski's stain, the examination of specimens stained by this method is preferable, except in the hands of an expert, to the examination of the fresh blood.

If fresh blood is to be examined, the patient's ear is carefully cleaned with alcohol, dried thoroughly, and a slight puncture made with a lancet or needle, and the first drop or two of blood allowed to flow away. A small drop is then taken on a slide which has been carefully cleaned and a coverglass placed over it. Specimens should be examined as soon as possible, but if carefully wrapped in paper can be carried for several hours without much danger of changes occurring which would obscure the plasmodia. The ear is preferable to the finger, especially in the case of children, as there is less pain, and the patient cannot watch the operator during the procedure. The blood should be examined with a one-twelfth oil-immersion objective and a one inch eye-piece. At least half an hour should be spent on the specimen before it is pronounced negative. For the examination of certain stages in the life-cycle of the malarial plasmodia, the examination of fresh blood is essential, but with our improved methods of staining, better results in diagnosis will be arrived at by the majority of physicians if stained specimens are used.

Examination of Stained Specimens.—There have been numerous methods proposed for the staining of the malarial plasmodia, the most valuable of which have been Romanowski's and its many modifications, such as Jenner's and Wright's. In 1902,¹ the writer described a method of staining which is simple and can be easily applied by the practicing physician. It is not as satisfactory in showing the finer struc-

¹ *New York Medical Journal*, September 13, 1902.

ture of the organisms as is Wright's method, but from a diagnostic standpoint it is easier of application in that the solution can be much more easily made, and the process is not so involved. It consists in the employment of two solutions: Solution A, a saturated aqueous solution of methyl violet B (Grübler's). This solution should be prepared with distilled water and should be at least three weeks old. Solution B, a five per cent. solution of aqueous eosin (Grübler's).

The method is as follows: Very thin blood smears are made upon perfectly clean coverglasses. These smears are hardened in absolute alcohol for five minutes, and are then carefully dried and stained with solution A for ten seconds; they are then thoroughly washed in water and stained with solution B for from three to five seconds. Specimens are then dried and mounted in Canada balsam. If the method is used as described the results are very satisfactory. The red blood corpuscles stain a beautiful dark blue while the parasites take a much lighter stain, the chromatin staining a deep red. The stain is especially useful in demonstrating the crescentic forms. These stain a very dark violet, the chromatin being reddish in color. The protoplasm of the polymorphonuclear leukocytes stains a dull pinkish violet, and the nucleus stains much less intensely. The granules of the eosinophiles stain dark red and the nucleus bright blue, while the protoplasm of the lymphocytes, both large and small, stain crimson violet and the nucleus pale blue.

Probably the most satisfactory of all staining methods for the malarial plasmodia is the modification of Romanowski's stain described by Wright. While the method of preparing the staining solution is somewhat complicated, a careful following of the directions will result satisfactorily. Numerous commercial houses have Wright's stain for sale, but as a rule the stains purchased in this way are unsatisfactory and cannot be relied upon. It is much better for the physician to make his own stain. Dr. H. R. Oliver has recently modified Wright's method slightly, and the staining solution as prepared by him gives very excellent results. The following is the method of preparation:

Add .5 gm. of soda bicarbonate to 100 Cc. of distilled water, dissolving thoroughly, and then add one gram of methylene blue (Grübler's) and heat for one hour in a sterilizer after the steam is up. After heating allow the mixture to cool. Make a 1 to 1000 solution of yellow eosin (Grübler's) and add this, stirring constantly, to the cooled methylene blue solution in the proportion of 500 Cc. of the eosin solution to 75 Cc. of the blue solution. This should be done, preferably, in a large porcelain dish. Let the mixture stand for a few minutes, and then filter through one small filter paper and save the residue. The residue, which is a crystalline, greenish-black powder, should be dried in a hot air oven and preserved. To make the staining solution, take .3 gm. of the residue and add 100 Cc. of pure methylic alcohol (Merck's) reagent. This should then be filtered, and to 80 Cc. of the filtrate add 20 Cc. of methylic alcohol. This is the stock solution ready for use. To stain, add a few drops of this solution to the preparation and let stand for two minutes, and then add enough distilled water to cause a slight metallic scum to form on the surface of the preparation. Specimens should then stand for two to ten minutes, be finally washed in running distilled water and mounted.

By this method all varieties of malarial parasites stain as follows: The protoplasm stains a robin's-egg blue, the vesicular portion of the nucleus remains unstained, while the chromatin stains a dark cherry red. The very young forms of the plasmodia—that is, the ring forms—are very distinctive, appearing as a bright blue ring at some portion of which is situated a dark cherry red dot marking the chromatin of the nucleus, the red blood cell being stained a very light red or brownish-yellow.

The only objection to the use of staining methods in the diagnosis of the malarial plasmodia is that certain other material, especially broken-down leukocytes or extraneous matter, may take the stain and be so situated within the red cell as to be mistaken for the organism. But to one who has once seen preparations stained by the methods described no mistake is possible in this direction. Particular care should be taken to make the blood smears very thin, and this is best done by the use of the method advocated by Cabot, which consists in using the ordinary ribbed rice cigarette paper, small pieces the width of the coverglass being cut parallel with the rib. The edge of the paper should then be passed quickly across the drop of the blood as it exudes from the ear, placed on the slide and drawn carefully along it. With practice, very even, thin smears can be obtained in this way.

The Therapeutic Test.—As Osler has well said, any fever which resists the action of quinine properly administered for more than four to five days, is not malarial in character. This fact is used as a means of diagnosis where for any reason an examination of the blood is impossible, but it must not be forgotten that quinine is capable of reducing the temperature in diseases other than malaria. In many instances, also, much harm may be done, especially in typhoid fever, which often resembles the continued æstivo-autumnal infections, and in which quinine is not only contra-indicated, but may be harmful.

Differential Diagnosis of the Various Forms of Malarial Fever.

—A differential diagnosis of the various types of malaria is most quickly and scientifically made by an examination of the blood. In this way the entire life-cycle of the tertian and quartan plasmodia may be studied, and the various types of plasmodia easily differentiated. Where, however, an examination of the blood for any reason is impracticable, the clinical symptoms may be of service in distinguishing the various types; thus, a typical tertian or quartan infection is easily differentiated by the time of the occurrence of the paroxysm and the study of the temperature chart alone, but it is impossible to differentiate a double tertian infection from a quotidian æstivo-autumnal infection in this way, and it is obvious that mixed infections cannot be differentiated by the clinical symptoms only. The temperature chart occurring in uncomplicated cases of tertian æstivo-autumnal fever is so characteristic that a differentiation of this form from other malarial infections can be easily made, but in all forms of malarial infections, the diagnosis should rest chiefly upon the result of blood examinations. While it may not appear to be of great importance to be always able to differentiate the exact type of malarial infection that is present, it surely is so from a scientific standpoint, and is often so practically. Grave mistakes have been made in considering a severe æstivo-autumnal infection as a mild tertian, and many lives have no doubt been lost by such mistakes in diagnosis. The æstivo-autumnal infections are

apt at any time to become pernicious and unless prompt treatment is instituted death is liable to follow. It can be easily seen that such an infection mistaken for tertian malaria, and treated by the administration of small doses of quinine, might result fatally.

While in uncomplicated tertian and quartan malaria the examination of the blood may not be absolutely essential in making a diagnosis, it is in the æstivo-autumnal infection, and it is especially in those presenting anomalous symptoms that such an examination is of the greatest service. In these cases the presence in the blood of the small intracellular ring forms, or of the crescents, demonstrates at once the character of the infection and enables us promptly to apply the proper treatment.

The differential diagnosis of the malarial fevers from other disease processes which may closely resemble them is only possible, in many instances, by the use of the microscope. This is especially true of the æstivo-autumnal infections which so often present anomalous symptoms resembling those of some other disease, that from a study of the clinical symptoms alone a diagnosis cannot be arrived at. There are a number of diseases with which malarial fevers, especially the irregular types, may be confused.

Typhoid Fever.—Perhaps no other disease has been so often confused with malaria as has typhoid fever. This was well borne out during our war with Spain. Clinically, the confusion regarding these two diseases has much to justify it. It is probable that a typical tertian or quartan infection is never suspected to be typhoid, or *vice versa*, but in the more irregular æstivo-autumnal infections this mistake has often been made. In regions in which æstivo-autumnal malaria is endemic, or supposed to be, it is a very common mistake to regard patients suffering from typhoid fever as victims of this type of malaria. This is because many cases of æstivo-autumnal infection present typhoid symptoms and a clinical differentiation is impossible. The mistake of considering a typhoid infection, however, as malarial, after quinine has been administered for several days, is inexcusable, for experience has shown that there is no malarial fever which will resist the action of quinine, when properly administered, for a period of over six or eight days. Despite this fact, many patients with typhoid fever in malarious regions are drenched with quinine under the suspicion that they are cases of æstivo-autumnal malaria. The differentiation of these two diseases depends upon the microscopic examination of the blood for the malarial plasmodia. Secondary to this is the therapeutic test by quinine. If parasites are present in the blood and the Widal test is negative, the diagnosis is at once established, and cases of combined infection are rare. The administration of quinine will remove the malarial element and the typhoid will pursue its ordinary course. During the decline of the temperature in typhoid cases a marked intermittent temperature may be observed which resembles very closely that of quotidian malarial infection. Chills also may occur at this time and a diagnosis of malaria is made. Unless supported by the finding of the malarial plasmodia in the blood, such a diagnosis is unjustifiable.

Yellow Fever.—In regions in which yellow fever is endemic, the differentiation of malaria from this disease is often exceedingly difficult unless a blood examination be made. The so-called bilious remittent type of æstivo-autumnal malaria is especially apt to simulate yellow fever, there

being present a yellow tint of the skin, severe vomiting, sometimes of dark material resembling "black vomit," while albumin appears in the urine. A patient presenting such a clinical picture in a yellow fever region is almost always thought to have yellow fever, and it is in these cases that an examination of the blood is of the greatest importance.

Tuberculosis.—In many cases tuberculosis is complicated by a streptococcus infection, and the temperature chart closely resembles that found in quotidian malarial infections. There may also be daily chills or chilly sensations, and the patient presents the facies so often observed in long-continued malarial infection. An examination of the sputum will generally result in the demonstration of the tubercle bacillus, while physical examination will show pulmonary lesions to be present. An examination of the blood, however, is essential, as not infrequently patients suffering from tuberculosis may contract malaria.

Hepatic Abscess.—In regions where amœbic dysentery is endemic, certain cases suffering from hepatic abscess may present symptoms which closely simulate those of malarial fever; thus there may be daily chills and a temperature curve, which, while it is that of sepsis, very closely simulates that of some of the forms of æstivo-autumnal infection. The chief clinical points in favor of hepatic abscess are enlargement of the liver and tenderness over the hepatic region, while the spleen is not enlarged. In malaria, enlargement of the spleen is almost always present. A history of dysentery can generally be obtained in cases of hepatic abscess. Examination of the blood will decide if malaria be present, while a leucocytosis will point toward a hepatic abscess.

Ulcerative Endocarditis.—The temperature chart in ulcerative endocarditis often resembles that of quotidian malaria, and Dock has published a very interesting case of this character. Examination of the heart will generally suffice to determine the nature of such cases, and if not, an examination of the blood will decide the question.

Cerebral Apoplexy.—The differential diagnosis between the comatose pernicious form of malaria and cerebral apoplexy is often extremely difficult unless a blood examination be made. The main clinical points to be relied upon in arriving at a diagnosis of malaria are high fever, although this is not constant, the age of the patient, and the splenic enlargement. An examination of the blood will generally decide the question at once.

Sunstroke.—Especially in tropical or sub-tropical regions, certain forms of pernicious malaria very closely resemble sunstroke. It should be remembered that in such regions the heat very often aggravates or brings on severe malarial paroxysms. It is therefore necessary to be sure in such cases whether or not a malarial infection be present and a microscopic examination of the blood is often our only means of arriving at a differential diagnosis.

Dysentery.—Malarial infections may occur with dysentery, and the removal of the malarial element in a certain proportion of such cases results in a rapid improvement of the dysenteric symptoms and their final disappearance. In view of the fact that malarial infection is capable of producing the clinical symptoms of dysentery, it is important that a differential diagnosis should be arrived at in regions where dysentery is endemic. An examination of the blood is therefore essential in every case of dysentery occurring in such regions.

Among other disease processes which may be confused with malaria, may be mentioned: septicæmia, pyæmia, diseases of the gall bladder or ducts, acute suppurative processes in any of the viscera, pneumonia, and Weil's disease. In all of these a careful examination of the blood is sometimes our only method of arriving at a differential diagnosis.

Prognosis.—The prognosis in cases of uncomplicated tertian and quartan malaria is good, but in the more severe æstivo-autumnal infections prognosis should be guarded. Osler has called attention to the fact that while in temperate climates it is well known that the prognosis in malaria is most favorable, still the vital statistics in some of our large cities show a greater death-rate for malaria than for typhoid fever. He says¹: "In the United States census report of 1890, which covers the six preceding years, the deaths from malarial fever in New York and Brooklyn were more numerous than from typhoid fever. In both these cities it is notorious that a death from true malaria is a great rarity. No more than three or four cases occur each year in the entire hospital practice of the city of New York." Nothing could illustrate more forcibly the immense importance of a scientific diagnosis of malaria fevers by an examination of the blood than does this quotation.

While the prognosis, as stated, in uncomplicated cases of tertian and quartan malaria is good, fatal cases of both these forms of fever have occurred, especially the quartan variety. As regards the prognosis of the æstivo-autumnal infections, certain factors have to be taken into consideration, such as locality, age, occupation, position in life, and physical condition. These factors apply with some force also to the prognosis of the simple intermittent fevers, but are especially important in the æstivo-autumnal infections.

In the tropics the prognosis in æstivo-autumnal infections is much more grave than in temperate regions, and in certain local regions these fevers are much more fatal than in others. The prognosis is most grave at the extremes of life. It is more grave in the poor than in those who are well-to-do, in the case of individuals in ill health than in those who are well nourished and healthy. Complications which are so frequent in æstivo-autumnal infections also have much to do with the prognosis, among the most serious being the various forms of nephritis, tuberculosis, pneumonia, dysentery, and the infectious fevers. The prognosis in the pernicious varieties of æstivo-autumnal infection should always be guarded, especially if the patient is seen after having suffered from several severe paroxysms, although even then if treatment be vigorously instituted the patient may recover. However, the pernicious symptoms may last for several days and despite all treatment, death ensue. The prognosis is very grave in the cerebral forms, especially the comatose form. While a large number of such cases recover under proper treatment, a great majority of the fatal cases of malaria suffer from this form of æstivo-autumnal infection. In the algid form the prognosis is almost as grave as in the cerebral forms, and not a few go on to a fatal termination despite all treatment. The prognosis is very grave in the choleraic form and also the pneumonic. In the dysenteric form the prognosis is always grave, depending upon the fact that the dysenteric symptoms have often masked

¹Article on "Malaria" in *Allbutt's System of Medicine*.

those of malaria for a considerable time and treatment is not instituted until too late.

In soldiers campaigning in tropical countries where pernicious forms of malaria are endemic, many deaths are often due to this cause, and the prognosis in such infections should also be very guarded.

In malarial cachexia where a change of locality cannot be secured the prognosis is always grave, death resulting not so much from the malarial infection as from some complicating disease. While under proper treatment a great majority of cases of æstivo-autumnal infection recover, unless quinine be administered for a long period of time relapses invariably occur, and one of these may prove fatal. It may be stated as an axiom that the prognosis in tertian and quartan malaria is good but in the æstivo-autumnal infections is always grave, as at any time during their course pernicious symptoms may develop and prove rapidly fatal.

Prophylaxis.—Prophylaxis in malarial disease is of much greater importance at this time than ever before in the history of such infections. We now know the etiological factor concerned in the production of the malarial fevers and their method of transmission, and we also know that proper methods of prophylaxis have already resulted in the disappearance of the infection from numerous localities.

The subject of prophylaxis may be divided into general and personal methods, all of which are directed against the mosquito. If it were possible to destroy all mosquitoes of the genus *Anopheles* in malarious localities, it is undoubtedly true that malaria would soon disappear. All our theories, regarding the transmission of the disease by water or any other way than by the aid of the mosquito, have been disproved and we now know that the prophylaxis of malaria consists in the destruction of this insect, or, if this is not possible, the protection of the individual from the bite of the infected insect.

General Prophylaxis.—General prophylaxis may be considered under the following divisions: (1) destruction of the mosquito; (2) isolation of the patient; (3) use of quinine.

1. Destruction of the Mosquito.—The mosquito is most easily destroyed during the larval stage, and many substances have been experimented with in the hope of obtaining one which would prove efficacious, being at the same time cheap and easily obtained. Howard, in 1892, published the results of his work upon the destruction of the mosquito larvæ by sprinkling a thin layer of kerosene upon the surface of the water in which they breed. This method is very efficacious, not only killing the larvæ in the water, but the mosquitoes when in the act of depositing their eggs. The method is especially applicable to collections of water which cannot be drained and which are not very large in extent. The quantity of kerosene used is approximately one ounce to fifteen square feet of surface, and as a rule the application does not need to be renewed more than once a month. This method has been used largely throughout the world and has proved of great value.

Of other substances which are capable of killing the larvæ, may be mentioned sulphurous oxide, permanganate of potash with hydrochloric acid, sulphate of iron or copper, carburet of lime, corrosive sublimate, formaline, cresol, certain aniline dyes, and coal-tar. It is obvious that most of these substances cannot be used in practice, the only one really

available being kerosene, but this agent cannot be employed in water which is used for drinking purposes unless in the case of large reservoirs where the water is drawn from the bottom.

The introduction of certain fish into reservoirs from which water is used for drinking purposes, and in which mosquitoes breed, has been suggested instead of the use of petroleum, and has been tried in some localities with success. The fish principally used have been carp and the common stickleback.

The most important of all methods of destroying the mosquito larvæ is that by drainage of their breeding places, and this is a method which can be employed over very large areas of country in which malaria is endemic, and which experimentally has proved to be of greatest service. In many regions in which the most virulent forms of malarial infection are endemic, drainage is feasible and can be carried out with but little trouble, although the expense is often a factor in the problem, and, as Celli says, "such methods for the destruction of the mosquitoes, while experimentally soluble, will only be practically so when economic interests desire it." Where drainage is impossible the breeding places of the mosquito may be filled up with loam, and it is very important in malarious localities to fill up all areas of depression in the surface of the land that cannot be adequately drained. Swampy areas, if not too large, can thus be filled in, and one of the greatest sources of mosquitoes removed.

Besides drainage and the filling up of areas which serve as breeding places for the mosquitoes, the formation of mosquito brigades, as suggested by Ross, is of the greatest service in limiting malarial infection. This consists essentially in detailing a certain number of men whose business it is to inspect the premises and destroy the larvæ in the small breeding grounds which harbor the *Anopheles*, such as domestic water receptacles, water butts, and tanks, the removal of small puddles in streets and yards, as well as empty tins, jars, broken bottles, or anything in which water collects, and in which the mosquitoes may breed. In the formation of such brigades the region to be covered is divided into portions, each portion being under the supervision of a certain number of men detailed for the purpose. Methods similar to this were pursued in Havana by Gorgas, resulting in the almost total disappearance of the yellow fever mosquito in that city. Garden wells, water barrels, and tanks, being prolific sources of mosquitoes, should be covered, preferably with wire mosquito-netting, thus preventing the laying of eggs and the development of the larvæ. If for any reason this is not possible, and the water is not used for drinking purposes, the surface should be sprinkled with kerosene oil.

In the adult stage the mosquito can be destroyed by various odors, fumes or gases. Among the odors may be mentioned turpentine, menthol and camphor. Among the fumes, tobacco, chrysanthemum powder, pyrethrum powder and the fresh leaves of eucalyptus; while among the gases, sulphuric oxide is very efficacious. In using any of these agents, however, it is very necessary that the air of the room should be saturated, as otherwise the insect may be simply stunned, and revive when the fresh air is admitted. The most useful of these agents is pyrethrum powder, which can be burned in rooms infected with mosquitoes, and which is very fatal to them.

2. Isolation of the Patient.—We have seen that the mosquito is necessary as an intermediate host in the life-cycle of the malarial plasmodia, and that the mosquito is infected by biting an individual suffering from malarial disease. From this it is obvious that if we can place the infected individual in a position where the mosquitoes cannot obtain access to him the transmission of the infection will be impossible. Theoretically, if every patient suffering from malaria could be screened from mosquitoes the disease would entirely disappear, but practically, the disease is of such a character that even when no symptoms are present the parasites may be present in the blood and the mosquitoes may become infected. In fact, in æstivo-autumnal infections the crescentic form of the organism, which really is the form intended to undergo its life-cycle in the mosquito, is frequently present in the blood when there are no symptoms of malaria, so that it is obvious that we cannot in this way entirely prevent malarial infection. Still, in the light of our present knowledge, the malarial fevers should be regarded as infectious and the patient should be isolated in a screened room. Not only is this isolation of importance to those surrounding the patient but also to himself, for if he is not protected from mosquitoes he is in constant danger of reinfection from the bites of the insects. Isolation of the patient is, therefore, of the greatest importance in the prophylaxis of malaria, and should be carried out, especially in regions where the more pernicious forms of the disease are endemic. Besides the isolation of the patient, Ross and Stephens have suggested as a method of general prophylaxis the segregation of certain classes of the population. This applies especially to Europeans living in the tropics. They suggest that the European quarter should not be built in the midst of the native villages in malarious localities, but should be situated at some distance and should be surrounded by the proper hygienic conditions, which it is impossible to obtain among a native population.

3. Use of Quinine.—The use of quinine as a general prophylactic measure, as suggested by Koch, is undoubtedly of value in malarial regions. As is well known, this drug destroys the malarial organisms, and if it were administered to all the natives of a malarial region it is probably true that malarial fever would gradually disappear. In other words, the malarial plasmodia present would be destroyed and thus the mosquitoes would not become infected upon biting the native population. Unfortunately, the cost of the drug precludes any general use of it in large localities, although theoretically the employment of it in general prophylaxis would be indicated.

Summing up, then, the methods of general prophylaxis which are most important are drainage and filling in of all depressed areas on the surface of the ground, the use of kerosene upon the surface of collections of water which cannot be drained, the formation of mosquito brigades for the purpose of cleaning or destroying the smaller breeding places of the mosquitoes, isolation of the patient, and the general use of quinine.

Personal Prophylaxis.—By personal prophylaxis we mean measures which the individual himself may take in order to prevent infection, or, in other words, to prevent being bitten by the mosquitoes. The use of mosquito-netting is of the greatest importance in malarious localities and no one should neglect the use of this means of prevention. The screening of the houses is also indicated, and the screening should be done most

carefully, every door and window being screened. If one is obliged to travel in malarial districts, the season of the year in which such fevers are less prevalent should be selected, if possible, and traveling should be done in the day-time. In selecting camp sites and sites for buildings, high, well-drained land should be chosen. The drinking-water should always be boiled, for although malaria is not transmitted in this way, the measure may prevent other diseases which would so deplete the system as to render it easily susceptible to malarial infection. If mosquitoes are numerous it is better to sleep above the ground floor. In tropical regions the use of punkas, or fans, as well as, where obtainable, electric fans, is serviceable in keeping away the mosquitoes. For the protection of the hands and face during the day, or when travelling at night, odorous substances may be employed, these being smeared on the skin and renewed when needed. Among the most useful are oil of pennyroyal, camphor, oil of eucalyptus, oil of anise, and kerosene. Pyrethrum powder should be burned before retiring, in rooms in which mosquitoes are present. Individuals in malarial localities should always sleep under a mosquito net.

One of the most important aids in personal prophylaxis is the use of quinine. It is borne out by the experience of all who have resided for any length of time in regions where malaria is endemic, that quinine exhibited daily in small doses is of the greatest value in preventing infection. The drug should be given in doses of from 5 to 6 grains (.30-.35 gm.) every day, or in larger doses, 8 to 10 grains (.50-.60 gm.), two or three times a week. In the vast majority of instances the prophylactic use of quinine will prevent malarial infection, but a few individuals, despite its use, succumb to the infection. Some individuals cannot take quinine regularly without suffering from disturbances of digestion or of the nervous system, and in such instances some substitute for it may be used, such as thiocol, or methylene blue. Neither of these agents, however, is as useful as quinine.

Treatment.—The treatment of malarial infection may be divided into hygienic and medicinal. While the medicinal is altogether the most important, hygienic measures should always be combined with it. Fortunately, in the malarial infections we have a specific which is invariably successful, when properly administered, in curing the disease. This specific is quinine, an alkaloid of cinchona, which was introduced into Europe nearly 260 years ago, and had probably been used by the natives in South America for many years before it was discovered by Europeans. Perhaps no drug known to the therapist is as true a specific in any disease as is quinine in malaria. When properly administered it will invariably destroy the malarial plasmodia and thus cure malarial infection. There are rare instances in which quinine seems to be powerless to limit the course of malarial infection, but a careful examination will prove that if it is administered in the proper manner it is efficient in these cases as in others. Thus, certain individuals cannot absorb quinine through the stomach, but in such persons the hypodermic administration of it will result in a cure of the infection, and thus it is that the successful treatment of malaria by quinine depends almost entirely upon the proper administration of the drug.

The mild intermittent malarial infections, such as the tertian and quartan, tend towards spontaneous recovery, which has already been

discussed. In many instances of infection by the tertian and quartan plasmodia, recovery may occur without the aid of medicinal measures, but it should be remembered that even these infections may become pernicious, and even if they do not, the occurrence of repeated paroxysms of the fever results in a diminution of the vitality of the patient, as evidenced by the anæmia which invariably accompanies such repeated attacks. Thus it is important that every malarial infection should be treated medicinally and not left for nature to cure.

Hygienic Treatment.—It is undoubtedly true that in all malarial infections, however mild, rest is most important, and the patient should be confined in bed until the active symptoms have disappeared. While this is not essential in some of the mildest tertian and quartan infections, it should always be followed out in cases of æstivo-autumnal infection. Treatment by quinine is always much more effective when the patient is confined to bed, recovery is always more rapid and permanent, and the danger of pernicious symptoms is also much lessened.

The diet should be light, while there are any active symptoms of malarial infection present, consisting of milk, soups, custards, soft boiled eggs, etc. A light diet should be persisted in until the temperature has been normal for at least a day, and then a more liberal diet is indicated. The more nutritious such a diet is the better, as in many cases of malarial infection the debility and anæmia following the paroxysms is remarkable.

It is a good plan in treating all malarial infections to secure a complete evacuation of the bowels coincident with or before the administration of quinine. The administration of calomel until the bowels move freely, not only serves to better the patient's condition, but also renders the action of quinine much more efficient. It hastens and favors the absorption of the drug.

In all cases of malarial infection the sick-room should be, if possible, in an upper story, well ventilated and thoroughly screened, thus limiting the chances of infection to others. Care should be taken that the room is not subject to draughts, and the patient should be guarded against any irritation, as in the most severe malarial infections, such as the æstivo-autumnal, the nervous irritability is apt to be very great.

Medicinal Treatment.—In the vast majority of malarial infections but one drug need be considered, that is, quinine, and by quinine any derivative of cinchona bark is meant. In considering the therapeutical uses of the derivatives of cinchona the following points should be discussed: (1) the action of quinine upon the malarial plasmodia; (2) the choice of preparations; (3) the time of administration; (4) the methods of administration; (5) the dosage; and (6) contra-indications to its administration.

1. The Action of Quinine Upon the Malarial Plasmodia.—Quinine exerts its beneficial action upon malarial infections by directly destroying the malarial plasmodia. Binz, in 1867, was the first to discover that the drug had a marked influence upon the parasites concerned in malaria, and his observations have been confirmed by every investigator who has studied the subject. Quinine causes a degeneration of the parasites, especially marked in the youngest organisms and most marked at the time of segmentation. Marchiafava and Bignami, from their careful study of the subject, conclude as follows: "Quinine acts upon the

malarial parasites in that phase of their life-cycle in which they are nourished and developed. When the nutritive activities cease by an arrest of the transformation of hæmoglobin into black pigment, and the reproductive phase begins, the quinine is ineffectual in its action."

In other words, the drug is most effective from the time of segmentation until pigmentation commences within the red blood corpuscles. Many observations upon the blood of patients, showing malarial parasites, to whom quinine has been administered, have shown that the chief changes consist in loss of amœboid motion and a granular degeneration of the endoglobular parasites. The red cell containing the parasite very often appears to be shrunken, as well as the parasite within it. The changes are most marked in the tertian and quartan organisms, but the same changes occur in the æstivo-autumnal varieties. In the latter, especially, the young unpigmented forms appear greatly shrunken, their protoplasm more or less granular, while amœboid motion is entirely lost. A study of stained specimens of malarial parasites after quinine has been administered, demonstrates more clearly than do fresh specimens the effect of the drug. In all such specimens the intensity of the stain is greatly diminished, and this loss of intensity is confined almost entirely to the chromatin substance of the nucleus, while the protoplasm stains more nearly as it does in the healthy organism. These changes prove that quinine acts directly upon the parasites causing the disease and that it is thus a true specific in malaria.

2. Choice of Preparation.—Of the ten or more salts of quinine which have been used in the treatment of malarial fevers, but two are really deserving of attention, in that they are of practical use. These are the sulphate and the dihydrochlorate or bimuriate of quinine. Of these two preparations, the dihydrochlorate is the more soluble, being dissolved in the proportion of 1 part to .96 parts of water, while the sulphate is only soluble in 1 to 9 parts of water. Of the two preparations, however, the sulphate is the more used, as it is the cheaper and can be procured most easily. Where it is desired to use the drug hypodermically or intravenously, the hydrochlorate should always be used.

3. Time of Administration.—The time of administration of quinine in malaria has been the subject of much discussion, but it may be said that in the tertian and quartan infections the drug should be given during the decline in temperature in one large dose, while in the æstivo-autumnal infections it should be administered in broken doses at equal intervals throughout the day. This subject has been very thoroughly discussed by Dock,¹ with whose conclusions the writer agrees. In tertian and quartan infections if the quinine is administered during the decline of the temperature, or at least, at the end of the apyrexia, in the vast majority the next paroxysm will be prevented, as the drug has thus been brought in contact with the youngest forms of the plasmodia, upon which it acts most vigorously. In all such cases the sulphate administered in solution dissolved in dilute sulphuric or hydrochloric acid is the most effective preparation. If given in this way, one drop of the acid should be used for each grain of quinine. If perchance, there should be double tertian or quartan infection, quinine administered at this time may not prevent

¹ *Journal of the American Medical Association*, July 29, 1899.

the succeeding paroxysm, and if this occurs, a second dose should be given at the same time, when almost invariably the paroxysms will cease. Quinine should not be discontinued, however, in the mildest cases, even after the paroxysms have ceased, but should be administered in doses of from 5 to 10 grains (.30 to .60 gm.) for at least a week. Only in this way can the return of the paroxysms be prevented.

In tertian and quartan infections the time of administration can be accurately determined by a study of the temperature chart, but this is not so in the more irregular æstivo-autumnal types. In these forms the period of intermission may not be indicated clearly in the temperature chart, and it is therefore necessary in order to combat the infection to give quinine in divided doses of from 5 to 10 grains (.30 to .60 gm.) at intervals of four to six hours until the temperature reaches normal. When this occurs, quinine may be administered in one large dose at bed-time or in smaller divided doses during the twenty-four hours. In pernicious and irregular forms of malarial fever, especially if caused by the æstivo-autumnal plasmodium, the administration of the drug cannot be delayed and it should be invariably given hypodermically.

4. Methods of Administration.—Quinine may be administered by the mouth, by the rectum, hypodermically and intravenously. If administered by the *mouth* it is best given in the form of solutions or capsules. Pills and tablets are very apt to be insoluble and therefore should not be administered. When possible, the drug should always be administered in solution, but on account of the bitter taste, which is very objectionable to some patients, capsules may be substituted instead of the solution.

The *rectal* administration of quinine, in the form of enemata or suppositories, has been advocated by some authorities but is most unsatisfactory. Absorption is very slow, and rectal irritability is almost certain to occur. When the drug is given in this way the dose should be one-half again as large as when given by the mouth.

In the pernicious forms of malarial fever quinine should be administered *hypodermically*, and this is also true in cases in which the drug cannot for certain reasons be administered by the mouth. The solution which is generally used is the following:

Dihydrochlorate of quinine.	gr. lxxv.....	5 gm.
Distilled water add.....	5iiss.....	10 gm.

In this solution 1 Cc., 15 m. contains grs. viiiss(.5 gm.) of quinine.

In giving hypodermic injections of quinine, the utmost care should be taken that the syringe be thoroughly sterilized and also the skin over the area in which the injection is made. The solution, also, should be sterile and freshly prepared. The best sites for the injection are the muscles of the back, gluteal region or the abdomen, the gluteal region being preferable. The injections should be made deeply into the muscles, and the wound made by the needle of the syringe covered with a small piece of cotton held in place by collodion. Despite the greatest care in giving hypodermic injections of this drug, much discomfort and pain is often caused, while if the operation has been carelessly done abscess formation is apt to result. If proper antiseptic methods are followed this generally may be avoided, although a considerable amount of induration is apt to occur around the site of the puncture.

Bacelli was the first to suggest the *intravenous* injection of quinine. Such a method of administration is indicated wherever the symptoms of malaria are so severe as to threaten grave peril to the patient, and should never be followed unless such symptoms are present. The solution used by him is made as follows:

Hydrochlorate of quinine	grs. xv	1.	gm.
Chloride of sodium	grs. xii75	gm.
Distilled water add	℥iiss	10.	Cc.

The entire amount is to be injected into a vein, preferably of the forearm, the most careful antiseptic measures being used to prevent infection.

5. The Dosage.—It is probably true that in the administration of quinine in malarial fevers too much of the drug is generally given. Very frequently quinine is administered in such large doses that a large proportion of it is simply wasted. In tertian and quartan infections a single dose of 15 grains (1 gm.) is amply sufficient to prevent the next paroxysm, while in the vast majority of æstivo-autumnal infections 30 grains (2 gm.) given in divided doses during the twenty-four hours will result in cure. When the drug is used hypodermically, a dose of 8 grains (.5 gm.) should be administered and repeated until about 24 grains (1.50 gm.) have been injected. In very severe infections more of the drug may be needed, but in my experience this amount is amply sufficient if administered promptly. When given intravenously, 15 grains (1 gm.) is sufficient.

Summary of Treatment.—In tertian and quartan infections quinine should be administered, preferably in solution and by the mouth in single doses of from 15 to 30 grains (1 to 2 gm.) during the decline of the temperature, and these doses repeated, if necessary, upon the following day. For a period of at least a month the drug should be given in gradually decreasing doses, thus preventing a recurrence. In æstivo-autumnal infections, quinine should be given in doses of 5 grains (.32 gm.) every four hours until the active symptoms have disappeared, and every five or six hours afterward for a period of three days. During the next week the drug should be administered in doses of 15 grains (1 gm.) on every other day and for at least two months thereafter upon every sixth day. If the drug is thus administered a definite cure of such infections may be predicted. The too rapid abandonment of treatment is one of the most serious mistakes which is made in the use of quinine. Relapses are almost sure to occur unless the drug be administered for a period of several weeks after the disappearance of active symptoms, and only in this way can we be positive that a recurrence of the disease will not take place.

Contra-indications to the Use of Quinine.—It has been the experience of most physicians that certain patients protest against the use of quinine, claiming that they are unable to take it. In most instances it is simply a matter of personal opinion, and if the physician be firm in insisting upon the use of the drug it will be found that such objections are generally the effect of imagination. However, in rare instances, the administration of quinine is contra-indicated, in that the drug produces such unpleasant and even dangerous symptoms that it cannot be safely used. Idiosyncrasy to quinine undoubtedly exists in certain patients, and therefore

some substitute for the drug has to be administered. Among these substitutes, none of which are as efficient as the drug itself, may be mentioned *euchinin*, an ethyl carbonate of quinine which is tasteless, and which may be given in about twice the dose of quinine, and *methylene blue*, which has been advocated by Ehrlich, and which may be useful in some cases, but is not nearly as effective as quinine. It is also not devoid of dangerous properties as it may produce severe diarrhoea, strangury, and albuminuria. It has been administered with good results in a few cases, in doses of from 8 to 15 grains (.5 to 1 gm.) during the twenty-four hours. For many years it has been supposed that the administration of quinine in large doses may result in hæmaturia. A careful investigation of the literature bearing upon this subject should convince any one that it is untrustworthy, and that true cases of hæmaturia following the administration of quinine are so rare as to be of practically no importance. The belief that hæmaturia may be produced in this manner is one of the medical superstitions which remain as a legacy to the profession, despite all scientific proof.

Treatment of Special Symptoms.—A cathartic dose of calomel should be given in all malarial fevers before the administration of quinine. During the acute stages symptomatic treatment should be adopted; thus, in the cold stage warm drinks, with the application of external heat in some form, are indicated; while in the warm stage, if the temperature reaches a dangerous point, baths of tepid or cold water should be given. Antipyretics, such as phenacetin, acetanilide, etc., should never be administered during the paroxysm of malarial fever, as they never do any good and may do much harm. If the vomiting be exhausting, or nervous symptoms be very pronounced, the hypodermic injection of morphine is indicated. Should cardiac weakness be present, suitable stimulants should be administered, such as hypodermic injections of ether, brandy, or strychnia. In the pernicious forms of æstivo-autumnal infection, symptomatic treatment is of the greatest importance; thus, if algid symptoms develop, stimulants should be freely administered, external heat applied by means of hot water and warm blankets, and collapse should be treated by hypodermic injections of brandy, strychnine, and by transfusion.

While the treatment of special symptoms during the malarial paroxysms is important, it should be remembered that unless quinine be given, all other treatment is useless, and that the prompt and proper administration of this drug will alone, in many instances, cause the disappearance of all alarming symptoms.

Treatment of Complications and Sequelæ.—The treatment of the complications occurring with the malarial fevers and the sequelæ following them does not require any discussion, it being the same as that pursued in all similar conditions.

Treatment of Malarial Cachexia.—The treatment of chronic malarial poisoning is most unsatisfactory if the patient remains in the locality in which he contracted this infection. While various remedial measures may be pursued, such as the administration of quinine, arsenic, and tonics of various kinds, but little result will follow unless a change of climate is secured. All these patients should, if possible, have a change of climate to a high, dry altitude, which is non-malarious,

and this will invariably do more for the patient than any therapeutic measure.

In conclusion, the fact is emphasized that no substitute for quinine can equal it in treatment of malaria, and that in the worst cases the proper administration of this drug will result in prompt recovery, provided the patient be seen in time. There are one or two substitutes for the drug which may be used in very rare instances where quinine is contra-indicated, but the writer believes with Osler, that, "the physician who at this day cannot treat malarial fever successfully with quinine, should abandon the practice of medicine."

CHAPTER XX.

BLACK-WATER FEVER.

BY J. W. W. STEPHENS, M.D. (CANTAB.), D.P.H.

Definition.—Black-water fever, or hæmoglobinuric fever; a disease occurring in tropical and subtropical countries, the chief symptom of which is the passing of hæmoglobin in the urine.

Distribution.—This is still imperfectly known. The number of cases recorded from any locality is unsatisfactory evidence as to the frequency in that locality, for we know of instances where cases have existed for years in a district and yet have been recorded only quite recently. We shall consider later the factors that determine its occurrence; one may here be mentioned: *viz.*, that as it is a disease affecting chiefly Europeans, at least in Africa, its occurrence in a particular region will depend, first, upon the presence of Europeans; and, secondly, whether such Europeans are subject to the conditions which give rise to it. Again we cannot say the disease is equally common in any two particular places; for in one case we may have a single record only, in others many. Bearing in mind these limitations to our knowledge of its distribution we may, in giving the following list, note any peculiarities.

In *North America* it has been recorded from Arkansas, Mississippi, Louisiana, Tennessee (?), Texas, Florida, Georgia, North Carolina, Alabama, South Carolina, Virginia. Among these records we find that it occurs mainly among white but occasionally also among colored persons. Although no doubt the statistical statements as to the mortality from malaria in the United States require to be accepted with caution, yet from the census returns it appears that these states are the most malarious in America. There are no exact data on record for judging of its frequency in any particular state.

In *Central America* it is recorded from Nicaragua, Costa Rica, and Venezuela.

West Indies: Cuba, Martinique and Guadeloupe, French, British, and Dutch (?) Guiana, Trinidad, and British Honduras. In Martinique it was recorded by French naval surgeons before 1850; but the only record from British Honduras occurs in 1905.

South America: The data here are very scanty, but it is recorded from Brazil and the Argentine Republic. Lutz in a personal communication says it occurs at S. Paolo, but it is rare there.

Europe and Asia Minor: The countries in which it is best known are Italy, Sicily, Sardinia, and Greece. It occurs at Merv (Russia), in Turkey, and, according to Marchoux, along the banks of the Danube and in the Caucasus. In Italy it is practically unknown in the North; a few cases occur in the Campagna; but it is in the South and especially in Sicily that it prevails, and here, too, malaria is most intense; thus, whereas the

mortality from malaria in North Italy is less than 1 in 10,000, in Sicily it is 7 to 8 per 10,000. It is apparently quite common in Greece, but we have no data as to its relation to malarial mortality there. It occurs in Palestine and with considerable severity in certain districts. It is not, however, known in Cyprus.

Africa: Its distribution is fairly well known, as the disease has here been carefully studied. It is found along the coast-line from the Senegal to the Orange rivers. It is found in the countries drained by the Congo, the Niger, and the Zambesi, and recently a few cases have occurred also in the upper reaches of the Blue and White Nile; in Senegambia, Gambia, Sierra Leone, Gold Coast, Lagos, Nigeria, Cameroons, Damara-land on the west, and British, German and Portuguese East Africa on the east. It occurs in Uganda and British Central Africa, but probably does not extend much further south than Delagoa Bay. In all these regions we may say that intense malaria is found. In Algeria it is by no means rare, but is unknown in Egypt, where malaria, at any rate among Europeans, is very uncommon. In Madagascar it has been described since 1851 by French naval surgeons. It is known also in Mauritius and Bourbon, but its occurrence in Zanzibar is doubtful.

India: Over the greater part of India it appears to be unknown. Foci occur in the Jeypore agency (Madras), in the Canara district (Bombay), and in the Duars (Bengal) the writer saw more cases in a fortnight than in the same time in Africa. It also occurs in the Terai (Bengal) and in Assam. According to Marchoux it exists in Burma.

Other Countries: It is recorded from Cochin China and Tonkin; also from Java (Tjilatjap), New Guinea (German), and single cases from British Malaya and New Hebrides. Finally, it occurs in Formosa, but not in Japan.

We believe that a consideration of these data, imperfect though they be, will show that the distribution of black-water fever and severe malaria is co-extensive. This holds good for the United States and for Italy, where the figures are probably fairly trustworthy. There is a further method of gauging malarial intensity which so far has been applied only in a few cases. Perhaps there is no more sensitive test of the malarial endemicity of a district, or endemic index, as we may term it, than the number of young native children with parasites in their blood (or with enlarged spleens). In many native villages of Africa for instance, 90 to 100 per cent. of children (under ten years of age) are infected with parasites, whereas if we take a similar determination in a large town or its suburbs the index will rapidly fall to 20, or 10, or even 0. It is possible by this means to measure marked changes in the malarial endemicity of districts which in no other way could make themselves evident.

By this means we believe it would be possible to compare the amount of malaria for instance in British Central Africa with that of Italy. We should at least get some definite numerical basis of comparison, far more accurate than we now possess. That malaria (and we are concerned with malaria here because we believe black-water fever to be malarial) is a deadly disease in the Congo and a trivial one in North Italy we can hardly doubt. On what this difference depends we cannot certainly say. It very possibly may be due to climatic differences, whatever that implies. In the contrast between malaria in North Italy and Sicily we

have a striking fact; and it is necessary to emphasize these differences in considering the relationship of malaria to black-water fever, because one of the objections frequently urged against its malarial origin is the fact that the distribution of the two diseases is not the same. But neither is the distribution of mild and severe malaria the same, a point to be remembered in considering the etiology of the disease. In considering the distribution of black-water, the circumstances under which a susceptible European population lives is important. For instance in many intensely malarious districts of Africa, segregated stations or cantonments have now been provided for the European residents. In other places Europeans still live under the evil conditions of infection which almost universally prevailed before a knowledge of the mosquito malaria cycle became well known. In such a segregated area malarial fever is reduced to a minimum, and black-water fever also disappears. If all Europeans were segregated from native dwellings, then we could conceivably get an intensely malarious region, as judged by the number of young children having parasites in their blood, without any black-water fever. For at least in the African negro, black-water is exceedingly rare, and if Europeans live away from natives instead of in their midst, as is too often still the case, then they will escape infection and consequently black-water fever. We have dwelt upon this point, because unless Europeans live under dangerous conditions black-water fever may be absent even in highly malarial districts.

It has rather been assumed so far that black-water fever is malarial in origin. What are the facts? Many hypotheses exist which need not concern us. We may refer to one which if true would be a simple solution of all difficulties that arise about this problem. Black-water fever implies hæmoglobin in the urine. Now, in cattle there is a well-known disease with hæmoglobin in the urine as one of its chief symptoms. This disease is due to a parasite, *piroplasma*; consequently, *ex hypothesi*, black-water fever in man is due to *piroplasma*. If all problems could be solved as simply as this, research into the nature of disease could be conducted in a library. Unfortunately there is not a shred of fact to support this simple hypothesis which the weary investigator has only too often wished true. That black-water fever is not a *piroplasmosis* is proved by the fact that *piroplasma* does not exist in the blood and tissues of cases of black-water fever, though repeatedly sought for by competent observers; and there is no question of its having been overlooked, for it is a parasite recognized without any difficulty. What, then, leaving aside this hypothesis, are the facts for and against the malarial origin of this disease?

First, there are arguments of a general nature but yet of much force.

1. There is no case on record of any one having contracted black-water fever who has not previously suffered from malaria and generally much malaria. Now if black-water were a disease *sui generis*, this would be very difficult of explanation; for were it, *e. g.*, *piroplasmosis*, then we should expect that an immigrant coming into a black-water district would at least occasionally contract black-water before he had contracted malaria; but this is contrary to the facts.

2. It is well known that in the tropics the disease is commonest among those who have suffered from repeated attacks of fever, even if these are

only slight in nature; and the frequency of attack according to the length of life in the tropics confirms this. Recent statistics on this point confirm the old ones of Berenger-Féraud, according to whom, of Europeans there are attacked 5.4 per cent. in their first year, 22.5 per cent. in their second year, 42.5 per cent. in their third year, 20 per cent. in their fourth year, and 4.8 per cent. in their fifth year. These figures conform with the experience of physicians practicing in the tropics at the present day, who well know that it is among the "old" residents that they see the cases. This peculiar distribution of black-water is strong evidence against the disease being due to any specific parasite, be it protozoön or bacterial.

3. Tropical Africa is admittedly one of the most malarial regions on the earth, and yet the mortality from malaria is slight when compared with that of black-water, as the following figures, compiled from the statistics relating to German troops in Africa over a period of years, show:

	Cases of malaria	Deaths from malaria	Cases of black-water fever	Deaths from black-water fever
G. E. Africa, April, 1897, to March, 1898	312	0	30	2
G. E. Africa, April, 1898, to March, 1899	345	1 (?)	33	3
G. E. Africa, April, 1899, to March, 1900	390	0	17	8 (or ? 11)
Cameroon, July, 1897, to June, 1898...	213	0	10	1
Cameroon, July, 1897, to June, 1898...	138	1	12	2
Cameroon, July, 1899, to June, 1900...	149	4	12	7
Cameroon, July, 1900, to June, 1901...	186	0	28	8
Togo, 1899 to 1900.....	72	2	5	5
Total.....	1805	8 (?)	147	36 (?39)

Thus malaria has a mortality of about 0.4 per cent., while that of black-water fever is about 25 per cent., *i. e.*, 60 times as great. We believe that the true explanation of these figures is that malaria is not a mild disease, but that its intensity is displayed in the form of black-water fever.

4. If black-water fever is malarial in origin, then those who protect themselves from malaria, either by careful personal prophylaxis (mosquito nets, adequate clothing, etc.), or by the taking of quinine, should be less attacked by black-water than those who are unprotected. The following data of A. Plehn support this view:

Attacks of malaria	Interval between attacks in months	Black-water cases	Interval between the cases in months	Deaths from black-water fever
287 70	2 5	31 6	18.5 74.0	10% about 0.

The first row consists of those who did not submit themselves to a systematic quinine prophylaxis, the second row of those who did, taking seven and one-half grains of quinine every fifth day.

5. Finally we come to the positive facts in favor of the malarial origin; and first as to the occurrence of malarial parasites in the blood of patients suffering from black-water. Here we may incidentally consider one of the

main arguments against the malarial origin; *viz.*, that in the majority of cases of black-water, parasites are not found, or, if they are, in so small a number as to have no causative relationship. The first part of this statement is true, and the observer who examines cases of black-water will be disappointed with the negative results of his examinations. The second proposition that the number of parasites, when they are found, bears no relationship to the severity of the symptoms, may or may not be true, but it is not necessarily so, for in malaria, at least in the tropics, we may get severe malaria with few or no parasites in the blood, and also the reverse condition: *viz.*, a considerable number of parasites and yet practically no symptoms. But we must consider the first part of this statement more closely, for it is only true as a general statement, and when analyzed carefully it is found not to accord with the facts. The following table is compiled from the records of observers who were well acquainted with the malarial parasite:

AUTHOR	DAY BEFORE HÆMOGLOBINURIA		DAY OF HÆMOGLOBINURIA		DAY AFTER ONSET	
	No. of cases	No. positive	No. of cases	No. positive	No. of cases	No. positive
A. Plehn.....	5	5	5	3	10	2
F. Plehn.....	0	0	21	18	10	3
Koch.....	5	5	8	6	6	1
Stephens and Christophers.....	1	1	9	2	16	0
Daniels.....	3	3	3	1	2	0
Panse.....	9	8	17	9	20	5
Total.....	23	22	63	39	64	11
Percentage Positive.....	95.6 per cent.		61.9 per cent.		17.1 per cent.	

Thus when the blood is examined *before* the attack, parasites are found in 95.6 per cent. of cases, on the day of the hæmoglobinuria in 61.9 per cent. of cases, and on the day after, when frequently the cases are first seen, in only 17.1 per cent. of cases. So that it appears that not only is black-water dependent on a malarial infection at some previous time, but that the relationship is a very close one, depending upon the actual presence of parasites immediately prior to the attack. To deny the significance of these parasites, as has been done, seems equivalent to denying the significance of parasites in an equivalent number of malaria cases, and to be contrary to common sense. One of the most striking characters of the blood examination in these cases is the rapidity with which parasites disappear.

Subsidiary evidence of malaria: In cases of true malaria it occasionally happens that parasites cannot be found in the blood, and perhaps this is most frequent during the pyrexial stages of the attacks. Again, in other cases parasites are so few in number that the argument that has been applied to black-water fever might equally well be applied here: *viz.*, that the number of parasites bears no relationship to the severity of the disease. Another cause of the absence of parasites in malaria is the previous administration of quinine; though the fever may still persist, yet no parasites can be found. In such cases we have means at our disposal by

which we can still diagnose malaria even though parasites are absent. These are two in number: (1) the presence of pigmented large mononuclearleukocytes; and (2) an increase in the percentage of large mononuclear leukocytes. The value of these is usually about 5 to 8 per cent., but in malaria the percentage is often markedly increased even up to 40 per cent., so that a value of 20 per cent., which is not uncommon, may be considered as fairly good evidence of malaria, especially as in such cases diligent search is almost always certain to detect pigmented leukocytes also. Christophers and the writer, in Africa, found that parasites were present only in 12.5 per cent., while by applying these two subsidiary tests evidence of malaria was found in 93.8 per cent. of cases; and it may be stated that care was taken to make adequate control observations among a number of persons selected as being liable to infection, but in these no such evidence of a malarial infection existed.

If we sum up now the actual evidence on which a malarial origin of black-water is based, we find that, apart from general considerations, (1) parasites *are* found in (nearly) all cases, provided the examination is made early enough; (2) that when parasites are absent, as is generally the case when the patients are seen late, still we have subsidiary evidence of malaria in (*a*) the presence of pigmented leukocytes and (*b*) the increased percentage of large mononuclear leukocytes. That parasites when found rapidly disappear is a well-known fact, but we must first consider another factor in the etiology of black-water fever. Black-water is common in Sicily, and it was here that Tomaselli first put forward the view that hæmoglobinuria in malaria is a quinine intoxication. This view has been vehemently controverted, but its adherents have steadily increased and at the present day it is impossible to deny that quinine can at least occasionally produce hæmoglobinuria. Patients who have themselves known that quinine certainly did induce an attack of hæmoglobinuria, have volunteered to undergo the experiment in hospital, and the result has been precisely as they stated. Thus it may now be taken as conclusively proved that quinine can induce black-water fever. It does not follow that all cases of black-water are due to quinine, sometimes in small and sometimes in large doses; but although absolute proof is wanting, yet any one who has carefully investigated the histories of cases of black-water and has observed patients in a hospital, can hardly doubt that quinine is often and indeed most often the exciting cause. Thus one patient had a typical malignant tertian malaria with a characteristic temperature chart and abundance of parasites. Quinine was administered, and after a doubtful interval hæmoglobinuria came on; then the parasites completely disappeared and were not found again till after death, in the spleen. Secondly, we have seen a patient admitted with black-water fever about midnight; the next day at noon the urine was clear; then quinine was given and the same afternoon black-water returned. Such cases are, when seen, very convincing; but it must be admitted that they are not as conclusive evidence of the quinine etiology as the experimental cases just mentioned. This quinine factor is probably one of the reasons why parasites disappear so rapidly; another probably is the actual destruction of red cells, which may affect especially those cells infected with parasites.

Whatever be the cause, it is very necessary to examine for parasites as early as possible. If they are to be found, a few hours' delay may mean a

negative examination. With regard to this quinine factor, two recent observations are worthy of note: (1) According to Marchoux, quinine is not excreted in the urine during the actual hæmoglobinuria, but reappears after this has ceased. This may imply that the retention of quinine is associated with the hæmoglobinuria, but though probable we have no actual chemical evidence of the truth of this hypothesis. (2) Poch records a case where, as the result of quinine administration, no actual hæmoglobinuria occurred, but only a diminution in red cells of 340,000. There are also other observations on record where quinine repeatedly induced black-water, yet on other occasions only gave rise to albuminuria. There are of course many objections to the quinine view; *viz.*: (1) The multitudes of people who take quinine and yet do not suffer from black-water. (2) Quinine will, we assume, produce an attack one day, but if administered on a subsequent day no such result occurs. We consider, however, that against the positive experimental evidence such objections cannot count, and the discrepancy means that we are in the dark as to the conditions of blood which allow of this hæmolytic action of quinine. We indeed should expect that if quinine has destroyed the less-resistant cells, then a second administration would not have the same result, as the residual cells are more resistant; but these are speculations about the resistance of red cells of which but little is known. We may sum up the etiology of black-water somewhat in this way: it is not a disease *per se*, but rather a condition of blood in which quinine, other drugs, cold, or even exertion, may produce a sudden destruction of red cells. The condition is produced only by malaria and generally by repeated small attacks insufficiently combated by quinine. In such cases of chronic malaria (*i. e.*, in those suffering from anæmia with repeated attacks of fever and repeated doses of quinine) black-water fever sooner or later almost certainly supervenes, at least in tropical climates. The two main factors in hæmoglobinuria are, then, malaria and quinine. While then we believe that the cause of black-water is known, yet it must be admitted that much work remains to be done in analyzing more minutely the exact blood condition which predisposes to an attack, and why especially quinine at one time will produce hæmolysis, and at another time will not.

Morbid Anatomy.—Spleen.—Melanin may be found in cells of the splenic reticulum in macrophages and in large mononuclear leukocytes. Hæmosiderin (yellow ochreous pigment) also is present. As already stated, pigmented leukocytes may be found here while absent in the blood during life; the same also holds good for parasites.

Liver.—Melanin occurs in endothelial cells and pigmented leukocytes in the capillaries: areas of necrotic liver-tissue are found laterally to the intralobular vein, and thrombi occur in the sublobular veins, and in these, pigmented leukocytes can be found.

Kidneys.—The epithelium of the convoluted tubes shows degeneration, and the lumen is filled with a granular mass; similar changes are found in the straight and collecting tubules. Melanin is not usually present.

Red Marrow.—Melanin is found in the capillary endothelium and in large branch cells, and also in leukocytes.

Brain.—Occasionally parasites occur here when absent elsewhere, but frequently no pigment can be found.

Symptoms.—As a rule the attack begins with a violent rigor; at the same time the temperature rapidly rises to 103° to 105° F. This is accompanied or preceded by general pain in the limbs, lassitude, and loss of appetite and not uncommonly there is great depression of spirits. On the other hand, sometimes the first indication the patient has that he is really unwell, is the passing of black water. There may be practically no other objective sign. It has been attempted to separate these cases from the previous ones and to regard them as true cases of quinine hæmoglobinuria, but no sharp line can be drawn between such cases and the severe ones with intense initial rigor. When the attack has set in—which the patient may have regarded as only a more than usually severe attack of fever—the urine next passed is found to be more or less black. The attack is accompanied by severe vomiting, which increases in severity and duration; the vomited matter is eventually almost entirely dark-green bile, and the persistence of this symptom exhausts the patient and is frequently of bad significance. Jaundice appears more or less early and eventually the body becomes of a light lemon-yellow color, though this may not be well marked in slight cases. The spleen and liver are usually enlarged and there may be considerable pain in these regions and over the kidneys. Tympanites is often a distressing symptom, and the epigastrium is painful on pressure. In severe cases hiccough troubles the patient much, and if there is a deficiency in the excretion of urine the prognosis is grave. Somnolence adds to the gravity and may progress into a fatal coma. The quantity of urine passed in mild cases is greater than normal, but a deficiency of urine is always unfavorable, for such cases may result in complete suppression. The passage of the urine is not uncommonly slightly painful. In a case of medium severity, however, after the initial symptoms, the temperature may quickly fall and the urine become free from hæmoglobin on the next day, still for some time retaining its “high” color. The fall of temperature is accompanied by sweating, and with an abatement of the other symptoms convalescence has already begun. In other cases, however, a relapse may occur with a rigor and a return of the hæmoglobinuria. Unusual complications are bloody diarrhoea or effusions of blood through the ear or nose. Occasionally parotitis is seen. Thrombosis of the heart is, according to Plehn, the commonest cause of death.

The Blood.—The drop of blood is often evidently yellow and “thin” in character; it has lost its viscosity, so that often, except by taking a large drop, it is difficult to procure satisfactory smears. If a drop of blood is allowed to clot in a small capillary tube, either hæmoglobinæmia or cholæmia may be found. Hæmoglobinuria is increasing—a fact which possibly supports the view that the hæmolysis really takes place for the most part in the kidneys. Microscopically, the blood does not show any appreciable evidence of the great destruction that may be going on; at most the red cells may look anæmic and have their central depressions enlarged; but there is no deformity of the red cells, as has been stated by some, such an appearance being due simply to badly made films. A stained specimen, *e. g.*, with the Romanowsky stain, may show two conditions—(1) polychromasia and (2) basophilia. These should be carefully looked for, as by some observers such a condition is supposed to indicate a further

tendency toward hæmolysis and to make administration of quinine dangerous. Further, normoblasts occur. The red cells may fall as low as a million in severe cases, and there is a corresponding deficiency in hæmoglobin.

Parasites.—We have said that as a rule parasites will not be found, as cases of black-water fever are not uncommonly first seen some time after the onset of the symptoms; but if examination is made early, parasites occur. In the absence of parasites careful search should be made through well-made films (most conveniently on the slide) for pigmented large mononuclear leukocytes. Occasionally they are plentiful, but as a rule careful search is required before they are found; and yet when absent from the blood during life, they may be found in the spleen postmortem.

Leukocytic Changes.—In malaria itself two conditions occur: first, there is a transient leukocytosis during the pyretic attack; and, secondly, a leukopenia, most marked during the apyrexia. In black-water, the leukocytosis appears to be more marked, possibly associated with the toxic condition, whatever be its cause. At this stage the polynuclear leukocytes may reach 90 per cent., and it is not until the leukocytosis ceases that the increase in the percentage of mononuclear leukocytes can be appreciated. This, which is most marked when there is leukopenia, may exceed 20 per cent., and, taken with the finding of pigmented leukocytes, is good evidence of a malarial infection when parasites are absent. The hæmoglobinuria generally supervenes some hours, one to five or more, after the taking of quinine, so that it is necessary to examine the blood early, as quinine itself frequently produces a rapid disappearance of parasites.

The Urine.—The urine is generally faintly alkaline in reaction, and the specific gravity less than normal. The color may vary from a very dark red to a brownish yellow, in which the spectroscope may be necessary to detect the hæmoglobin. A character of the urine in severe cases is the large amount of sediment, which consists of a yellowish granular material, the granules varying in size from 1 to 7μ and appearing to consist of broken-down blood-cells. In the sediment a few reddish crystals of hæmatoidin occur. The darkness of the urine is not always a safe guide to the amount of hæmoglobin present, and often a centrifugalized urine will, on examination with the spectroscope, prove to be free from blood-pigment. Blood corpuscles are rare; the condition is one of hæmoglobinuria and not hæmaturia. A spectroscopic examination of the urine, diluted if necessary, shows the double band of oxyhæmoglobin or the bands of methæmoglobin. Urobilin is commonly present; it is best detected in the form of zinc-urobilin. Further research is required both on the pigments and on the proteid constituents of the urine. The amount of albumin is often so great that, after boiling, the contents of the test-tube set solid and may be inverted without spilling. Bile-pigments are generally absent, but may appear with the onset of the fever, to be replaced later by oxyhæmoglobin.

Diagnosis.—The disease, which may present the greatest difficulty in diagnosis, is perhaps yellow fever. But the points of distinction are many. The history of many previous attacks of malaria and of the administration of quinine, point to black-water. In mild cases of yellow fever we do not get a definite hæmoglobinuria, but at most a slight albuminuria. Fre-

quently from past attacks of malaria the spleen is enlarged; in yellow fever it is not. In yellow fever of greater severity there is the pronounced suffusion of the face, the dry tongue with red tip, and later the pronounced icterus and black vomit. In black-water fever also there is icterus, but the other features are wanting, and the black vomit of severe cases is lacking. In black-water, on the contrary, we get almost pure dark-green bile. Finally we have in yellow fever the characteristic relationship of the pulse to the temperature, *viz.*, that the pulse does not increase, but decreases in frequency with the increase in temperature. The presence of parasites does not exclude yellow fever, but in practice there should be but little difficulty in distinguishing between the two diseases. Postmortem the distinction is equally well marked. In black-water fever the spleen and liver are usually enlarged, may be pigmented, and parasites may be found microscopically. In yellow fever the liver is only slightly if at all enlarged, and presents on section a characteristic box-wood color. In black-water fever the liver is commonly enlarged, and is also icteric, though the tint is not the same as that in yellow fever. Ecchymoses occur in the gall-bladder in yellow fever; they have not been noted in black-water. The body presents flecks and true hemorrhages in yellow fever, the stomach and intestines show a considerable amount of hyperæmia or hemorrhages, and the stomach often contains dark, slimy masses.

Prognosis.—Mild attacks are generally recovered from rapidly. The mortality may be set down roughly as from 10 to 20 per cent. It is advisable that the patient who has once suffered from black-water should not return to the tropics unless he makes up his mind that he will undertake strict prophylaxis against malaria, either by protecting himself scrupulously against mosquitoes, or by a strict quinine prophylaxis such as 5 grains every morning or 10 to 15 grains every tenth day.

Treatment.—If the quinine view of black-water be correct the question arises as to how black-water fever is to be treated. Whether or not we believe this view, the result of experience is undoubtedly against the administration of quinine. As parasites rapidly disappear, it is not generally necessary in these cases to administer quinine. In all cases a careful blood examination should be made, and if parasites still persist with a continuance of the fever, then the question must be carefully weighed as to whether quinine is to be given or not. If it can be avoided we should say it is better to abstain; but if it is judged advisable from the continuance of the fever, then it should be commenced in quite small doses—one or two grains at a time. According to some there is less risk if it is administered subcutaneously, and if this dose is well borne, then it should be increased to five grains and from this upward. In some cases methylene blue may be tried, but this lacks the efficiency of quinine. Should the black-water return after quinine, a second attempt may be made, but it is dangerous, for in one of Koch's cases the result was always the same, and finally the symptoms became so aggravated that quinine had to be withheld. This, however, does not always occur, and a second attempt may be successful; if not, there is no course open but to trust to the fever subsiding.

The general treatment is, however, the most important matter. The bowels should be kept open by calomel, jalap, or enemata. Champagne is frequently necessary and is often retained when all food is rejected.

The thirst should be allayed with ice, if procurable, and nutrient enemata given if necessary. The vomiting is often very troublesome, and for this Hearsey uses morphia (gr. $\frac{1}{2}$, gm. 0.03) hypodermically. Hearsey treats his cases with a mixture containing bicarbonate of soda (grs. 10, gm. 0.6) and perchloride of mercury (gr. $\frac{1}{30}$, gm. 0.002) in each dose, given every two hours. Acid drinks are at the same time prohibited. We do not consider that this treatment has the specific value that the author claims for it, but it may well be tried. Doering alleviates vomiting by the use of Carlsbad salts, a teaspoonful in water, repeating the dose if vomited. Injections, intravenous or subcutaneous, of normal saline solution, have been used with good effect by some. Vincent recommends calcium chloride to prevent the susceptibility to black-water and also during the attack (4-6 gm. daily or 1-2 gm. injected subcutaneously in saline solution). Dannermann uses a decoction of a native African fever remedy, the leaves of *Combretus Raimbanthus*. (Decoct. fol. combreti 24 parts, water 1,500 parts, used as a tea during the day.) To promote diuresis potassium acetate is used.

The symptoms arising from the kidney, heart, and nervous system, are those which require especial attention. General treatment and good nursing especially are of the greatest importance, and to these must be attributed the successful treatment, and not to any specific value of the various remedies advocated.

CHAPTER XXI.

TRYPANOSOMIASIS.

By COL. DAVID BRUCE, C. B., F. R. S., R. A. M. C.

Introduction.—The group of diseases which comes under the term Trypanosomiasis attracted little attention until a few years ago; now, it seems to be usurping the position of interest held during the last quarter of a century by the bacteria.¹ Diseases caused by trypanosomes are found over a large area of the earth's surface, from South America, through Africa, Southern Europe, Persia to India, Burma, China, and the Philippines,² and affect many kinds of animals, including man. These diseases are all caused by the presence in the blood and body-fluids of species of flagellated protozoa belonging to the genus *Trypanosoma*. A trypanosome consists of a single cell, and in its best known form is a sinuous worm-like creature, provided with a macronucleus and a micronucleus or blepharoplast, a long terminal flagellum, and a narrow fin-like membrane, continuous with the flagellum and running the whole length of the body. The end from which the flagellum protrudes is usually called the anterior; the other end, near which as a rule is situated the micronucleus, the posterior. When alive this hæmatozoon is extremely rapid in its movements, constantly dashing about and lashing the red blood corpuscles into motion with its flagellum, and it swims equally well with either extremity in front. These parasites give rise to an extreme variety of diseases, sometimes so acute as to cause death in a few days, at other times so chronic as to take several years to kill. Some of the species, again, appear to live in the blood of their hosts without causing any perceptible disease, and especially is this so in those species which live in fish, frogs, and other cold-blooded animals. As to how the trypanosome damages its host is not very clearly known at present, but the probability is that it gives rise to the presence of small quantities of toxins in the blood and so causes, in some animals, chronic inflammatory processes, or in others extensive and rapid destruction of the blood corpuscles. However the damage is done, trypanosomiasis is extremely fatal in man and the domestic animals, such as the horse, dog, and ox. Large native populations in Central Africa are being swept away at this moment by this plague, and great tracts of country are rendered uninhabitable for man and the domestic animals. In this paper a brief historical sketch and description of the more important trypanosomes and the diseases they give rise to, with special reference to that species which affects man, are given.

¹ *Trypanosomes et Trypanosomiasis* par A. Laveran et F. Mesnil, Masson et Cie, Paris, 1904, p. 419.

² "Report on Trypanosomiasis," etc., by W. E. Musgrave and M. T. Clegg, *Report of the Superintendent of Government Laboratories in the Philippine Islands*, 1903, Bureau of Insular Affairs, War Department, United States.

TRYPANOSOMA LEWISI.

The Rat Trypanosome.—The earlier discoveries of trypanosomes in the blood of fish and frogs, dating from the year 1841, may be passed over. They were interesting to the zoölogist, but having at that time no obvious bearing on the causation of disease, did not attract the attention of medical men. For about forty years little or no progress was made in the subject until Surgeon-Major T. R. Lewis,¹ F.R.S., Royal Army Medical Corps, made an important observation by finding flagellated organisms in the blood of rats. This interesting discovery may be described in his own words. He says that having been directed to make certain enquiries regarding the nature of the sometimes designated "spirillum fever," which prevailed in Bombay during the early part of 1877, he had occasion to examine the blood of a considerable number of animals, and, in July of that year, detected spirillum-like organisms in the blood of healthy rats. In some instances these were so numerous that the blood, when examined under a high power, seemed to quiver with life. On careful focussing, it was ascertained that each organism consisted of a body portion, and of an extension of it in the form of a gradually tapering, long flagellum. They were found in two species of rats—*Mus. decumanus* and *Mus. rufescens*—and in 29 per cent. of the animals examined. Lewis naturally fell into the error, when Dr. Griffith Evans,² the Chief of the Veterinary Department in Madras, discovered similar organisms in the blood of horses suffering from surra, of considering that the two parasites were identical. With better microscopes than Lewis possessed, it can now be seen that the morphology of the rat trypanosome differs much from that of surra. The only animal in the blood of which the former will live is the rat. This rat trypanosome is distributed, broadly speaking, all over the world; and even in Uganda, in Central Africa, we found numbers of the common field rat harboring it. The rat trypanosome does not appear to give rise to any symptoms of disease, although their numbers in the blood may be exceedingly numerous.

TRYPANOSOMA EVANSI.³

Surra.—This trypanosome was discovered in 1880, as mentioned above, by Evans.⁴ Surra is mainly an Indian disease, occurring in the Punjab and in Burma. The disease usually appears during the rainy season, and disappears gradually with the advent of the cold, dry weather. Places in which surra is reported to occur naturally, are mostly situated close to swamps or alongside rivers, and liable to inundation during the rains. The horse and mule are most susceptible to surra, the dog coming next, and these three always succumb to the disease. The camel is supposed

¹Lewis, "Flagellated Organisms in the Blood of Healthy Rats," *Quart. Journ. Micr. Sc.*, Vol. XIX, January, 1879, 109.

²Evans, "On a Horse Disease in India Known as 'Surra,' Probably Due to a Hæmatozoon," *Vet. Journ.*, Vols. XIII and XIV, 1881–1882.

³Steel, J. H., *Report on his Investigation into an Obscure and Fatal Disease among Transport Mules in British Burma*, 1885.

⁴Evans, G., *Report on Surra*, Published by the Punjab Government, 1880.

to live for three years after becoming infected, while the ox generally recovers after some five or six months. Rogers¹ states that surra is carried from sick to healthy animals by species of tabanus, and other writers have stated that stomoxys also acts as an infecting agent. Surra is very closely related to the next disease—nagana—and, in fact, is considered by many to be identical.

TRYPANOSOMA BRUCEI.²

Nagana or Tsetse-fly Disease.—As the writer of this article had the good fortune to discover this species of trypanosome in 1894, perhaps a few words of personal experience will not come amiss. In October, 1894, when serving in Natal, South Africa, the governor of that colony, the Hon. Sir Walter Hely-Hutchinson, G.C.M.G., asked me to go to Zululand to report on a disease which was causing severe loss among the native cattle. The native name of the disease was nagana. At this time no suspicion that nagana and the tsetse-fly disease were identical was entertained. The writer at once proceeded to Zululand and after a month's travelling by ox-wagon from Eshowe, the capital of that country, arrived in the infected area. A small laboratory having been set up and some of the affected cattle obtained from the surrounding natives, examination by the ordinary bacteriological methods was begun. The animals were emaciated, with staring hair, some fever, and sometimes œdema of the subcutaneous tissues of the neck. Examination of the blood and organs for bacteria by microscopic and cultural methods produced no result. At this time it was my custom, when starting on the study of a new disease, to make a careful daily examination of the blood of the living animal, enumerating the number of the red and white blood corpuscles and estimating the percentage of the various varieties of leukocytes. After a few days of this blood examination it was noted that there was sometimes to be seen a peculiar stained body, having something of the appearance of an artistic dolphin, lying among the red blood corpuscles. It must be remembered that the trypanosomes are usually found in very small numbers in cattle, so that it is only after a long search that a single one can be found. It was thought at first that this small, peculiarly shaped object was an accidental appearance due to the stain, but thinking that if the body was a parasite, it might show motion, several specimens of fresh blood were examined. A long search was rewarded by finding a very active body, wriggling and twisting about with great energy and dashing in and out among the red blood corpuscles. It was the first time the writer had seen a trypanosome, and, as then there was little or no literature on the subject of these parasites, it was difficult to know how to place it. It seemed that it must be a filaria, but having

¹ Rogers. "The transmission of the *Trypanosoma evansi* by horse-flies, and other experiments pointing to the probable identity of Surra of India and Nagana or Tsetse-fly Disease of Africa." *Proc. Roy. Soc.*, Vol. LXVIII, March 14, 1901.

² Bradford and Plimmer, "The *Trypanosoma Brucei*, the Organism found in Nagana or Tsetse-fly Disease," *Quarterly Journal of Microscopical Science*, Vol. XLV, 1902.

compared the description and drawing of the rat trypanosome in Lewis's book,¹ with my parasite, it was concluded that it was a trypanosome. But there was no proof that the parasite was the cause of nagana; it occurred only in small numbers in the blood of the cattle, and the rat trypanosome lives as a harmless guest in healthy animals. Therefore, the blood of the infected cattle was inoculated into horses and dogs.² The disease in the horse and dog is much more acute than in the ox. In a few days the blood, especially of the dog, was found to be teeming with thousands of trypanosomes. It, therefore, began to appear probable that this parasite might be the cause of nagana. At that time there was no suspicion that this disease among the native cattle, occurring in kraals situated many miles from the "Fly country," was the same disease as that known to travellers as the tsetse-fly disease. The work at this time was being done on the summit of a mountain called Ubombo, some 2,000 feet above the surrounding low country. The low country to the east of the mountain was known to be infected with the tsetse-fly, and having often read, in Livingstone's and other books of travel and hunting, about this disease, it was determined to take a few animals into this "Fly country" and see what the disease was like. Two young oxen, a horse, and several dogs, were taken into the heart of the "Fly country." After being there a fortnight the animals were brought back to the top of the mountain and examined in the usual way; their temperature taken, their blood examined, and any symptoms that might occur noted. It was found that the blood of these animals affected with the tsetse-fly disease contained the same parasite as that found in nagana. In this way, after many experiments and many observations, it was forced upon me that the two diseases, nagana and tsetse-fly, were one and the same. It is a characteristic of this species of tsetse-fly, *Glossina morsitans*, that at rare intervals, probably due to long continued drought, it overspreads its usual bounds to a distance sometimes fifty or sixty miles, and so sets up an epidemic among the native cattle in a previously healthy district. This was the case in 1894; the disease had overspread its natural bounds and given rise to a wide spreading epidemic among the cattle to a distance of sixty miles.

When it was once established that the two diseases were the same, experiments were made to find out how the animals became infected, whether the fly was the carrier or a mere concomitant of the low lying unhealthy district, and, if a carrier, if it was the only carrier of the disease from sick to healthy animals. Horses taken down into the "Fly country," and not allowed to feed or drink there, took the disease. Bundles of grass and supplies of water, brought from the most deadly parts of the "Fly country" to the top of Ubombo and there used as fodder for healthy horses, failed to convey the disease. Tsetse-flies, caught in the low country and kept in cages on the top of the mountain, when fed on affected animals were capable of giving rise to the disease in healthy animals up to forty-

¹Lewis, T. B., *Physiological and Pathological Researches*, Published by Lewis Memorial Committee, 1888.

²Bruce, D., *Preliminary Report on the Tsetse-fly Disease or Nagana in Zululand*, Durban, Natal, 1895, *Further Report*, Printed for the Royal Society by Harrison & Sons, London, 1896; *Appendix to Further Report*, Harrison & Sons, 1903.

eight hours after feeding. Tsetse-flies, brought up from the low country and placed straightway upon healthy animals, were also found to give rise to the disease. The flies were never found to retain the power of infection for more than forty-eight hours after they had fed upon a sick animal, so that if wild tsetse-flies were brought up from the low country, kept without food for three days and then fed on a healthy dog, they never gave rise to the disease. In this way it was proved that the tsetse-fly, and it alone, was the carrier of nagana. Then the question arose as to where the tsetse-flies obtained the trypanosomes. The flies lived among the wild animals, such as buffaloes, koodoos, and other species of antelopes, and, naturally, fed on them. It seemed that, in all probability, the reservoir of the disease was to be found in the wild animals. Therefore all the different species of wild animals obtainable were examined both by the injection of their blood into healthy susceptible animals, and also by direct microscopic examination of the blood itself. In this way it was discovered that many of the wild animals harbored this trypanosome in their blood. The parasites were never numerous, so that it was only after a long search that they could be discovered by the microscope alone. The wild animals did not seem to be affected by the trypanosome in any way; they showed no signs or symptoms of the disease, and it therefore appeared probable that the trypanosomes lived in their blood as harmless guests, just as the trypanosome of the rat lives in the blood of that animal. The flies were examined at various times after feeding, to see if there was any kind of metamorphosis taking place within the body cavity. But no such evidence could at any time be discovered. The trypanosomes can be found alive and wriggling vigorously in the œsophagus and stomach for about five days after feeding; as long, in fact, as the smallest quantity of blood remains undigested. No living trypanosomes are ever found in the intestines or droppings, and the latter, on many occasions injected into healthy animals, failed in every instance to give rise to the disease. The fly then can only be regarded as a mechanical carrier of the trypanosome and not as the specific intermediate host. If this is so it seems strange that the tsetse-fly should be the only carrier of the disease. That this is so is evident from the fact that a huge experiment to prove this has been going on in nature in South Africa from time immemorial. Here and there are tracts of country called "Fly belts." They are called "Fly belts" on account of the presence of the tsetse-fly. Outside the fly zone there may be a tract of country differing little in physical characters from "Fly country," where many species of biting flies abound, but no tsetse. Here the wild animals carrying the trypanosome in their blood are also found. Horses and cattle remain quite healthy in such a country, consorting with wildebeeste and other antelope, and constantly exposed to the bites of tabanidæ, stomoxys, and other biting flies. During a stay of two years on the top of the Ubombo, within an hour's march of the "Fly country," although healthy animals lived side by side with those affected with nagana, not a single case of natural infection took place, albeit there were many ordinary biting flies about. On the other hand, if a horse or dog was taken into a "Fly belt," even for a few hours, it almost certainly became infected. It seems then to be a fact almost beyond suspicion that the disease known as nagana or the tsetse-fly disease is carried by *Glossina* and by no other genus of biting flies in Africa. It is strange that some

phenomenon similar to this should not have been brought out in regard to the Indian trypanosome disease. It is evident that surra has a peculiar distribution, and it seems probable that this will be found to depend upon the distribution of some species or genus of biting insect.

Nagana affects a large variety of species of animals. With the exception of the baboon, it is fatal to monkeys, horses, mules, donkeys, cattle, dogs, cats, rabbits, guinea-pigs, rats, mice, and other animals. It is a peculiar circumstance that man is one of the few animals immune to this disease. No case has yet been recorded of the occurrence of nagana in man, either among the natives living in the "Fly country," or in Europeans who live or go into the "Fly country" in search of game. Nagana has probably been studied more than any other trypanosome disease, due to the writer having sent to England, in 1898, dogs with the trypanosomes in their blood. Descendants of these trypanosomes have found their way to many laboratories, even in America.

TRYPANOSOMA GAMBIENSE. HUMAN TRYPANOSOMIASIS. SLEEPING SICKNESS.

Historical.—The *Trypanosoma Gambiense* was first described by the late Dr. J. E. Dutton. The parasites occurred in the blood of an Englishman who had been employed for six years as master of a government boat plying on the Gambia River, West Africa. He was admitted into the hospital, at Bathurst, on the 10th of May, 1901, under the care of Dr. R. M. Forde, Colonial Surgeon.¹ Dr. Forde examined his blood and saw actively moving worm-like bodies, which he was unable to identify; he, therefore, asked Dr. Dutton to assist him in the diagnosis. In the meantime, the patient had been invalided to England, where he was for some time under treatment in a hospital in Liverpool. He returned to Bathurst in December, 1901, and on the 15th, Dr. Dutton examined his blood and saw the trypanosome, which he described and named.² At this time no suspicion existed that the so-called trypanosoma fever or Gambia fever had any relation to sleeping sickness. This discovery of trypanosomes in the blood of man awakened a great deal of interest, and Dr. Dutton, accompanied by Dr. J. L. Todd, was sent out to Senegambia to make further investigations. They arrived at Bathurst on the 2nd of September, 1902, and remained on the West Coast for nearly a year. They examined 1,043 natives in the Gambia, and found the parasite in 6 cases only. They sum up their report by saying that, taking all the facts into consideration, they believe the disease, as it occurs in natives, to be a peculiarly mild one, and that it is at present impossible to recognize it clinically, and they suggest the possibility that the natives in this disease may bear the same relation to the Europeans as does the wild game of Central Africa to domestic animals in the tsetse-fly disease.³

¹Forde, R. M., *The Journal of Tropical Medicine*, September 1, 1902.

²Dutton, J. E., "Trypanosome Occurring in the Blood of Man," *Thompson-Yates Laboratory Reports*, Vol. IV, pt. II, 1902.

³Dutton and Todd, *First Report of the Expedition to Senegambia*, Liverpool School of Tropical Medicine, Memoir XI, 1902.

In the beginning of 1903, Dr. C. J. Baker¹ noted the presence of trypanosomes in three cases in the blood of man in Entebbe, Uganda. Shortly before this Dr. Castellani,² a member of the Commission sent out to Uganda by the Royal Society, London, for the purpose of investigating sleeping sickness, had observed these hæmatozoa in the cerebro-spinal fluid of 5 cases of sleeping sickness, and in 1 of these he had also seen them in the blood. This was the first time trypanosomes had been seen in the blood of recognized cases of sleeping sickness. When the writer arrived in Uganda, on March 16, 1903, for the purpose of continuing the investigation of this disease, Castellani described his findings, and, as was to be expected after the work on nagana, the observation was very striking. Castellani, who intended to leave immediately for England, consented to stay a week or two longer, in order that we might pursue this particular point. He remained in Entebbe for three weeks, and during this time we examined 22 cases of sleeping sickness and found the trypanosomes in 15, about 70 per cent.

From this time the history of the *Trypanosoma Gambiense* is merged in that of sleeping sickness and most writers are now agreed that in all probability the so-called trypanosoma fever or Gambia fever is merely the first, and sleeping sickness the last stage of human trypanosomiasis. This, however, being still a matter of dispute, will be discussed more fully later on.

This then is a short account of the *Trypanosoma Gambiense* from its discovery as a supposed harmless parasite in the blood of natives on the Gambia, to its apotheosis as the cause of the terribly fatal sleeping sickness.

Human Trypanosomiasis or Sleeping Sickness.—The history of the disease itself may be given in a few words. Human trypanosomiasis or sleeping sickness has been known for more than a hundred years on the West Coast of Africa, and has attracted a good deal of interest and curiosity on account of the peculiar symptoms of lethargy which developed and which gave rise to the name of sleeping sickness. The disease, although of an apparently infectious nature in its native haunts, was found to lose its power of spreading from man to man upon removal to a non-endemic area. Thus much interest was raised by the fact that slaves introduced to other countries from the West Coast often died of sleeping sickness, but the disease never spread to their neighbors—never became endemic. Different theories were held as to its causation, some holding it to be a food intoxication, others blaming various kinds of bacteria. As an upholder of the former Ziemann³ may be cited; of the latter, Battencourt⁴ and Castellani.⁵ Another theory which seemed plausible was that the disease was caused by *Filaria perstans* and found its advocate in Sir Patrick Manson.⁶ All these speculations have been proved to be unfounded, by the discovery that the causal agent in this disease is really the *Trypanosoma Gambiense*.

¹ Baker, C. J., "Three cases of *Trypanosoma* in Man in Entebbe, Uganda." *British Medical Journal*, May 30, 1903, p. 1245.

² Castellani, "Presence of *Trypanosoma* in Sleeping Sickness," *Royal Society, Reports of the Sleeping Sickness Commission*, 1903. Harrison & Sons, London.

³ Ziemann, H., *Centralblatt f. Bakter*, Orig. Vol. XXXII, 1903.

⁴ Battencourt, A., *Doença do Somno*, Lisbonne, 1901.

⁵ Castellani, A., *British Medical Journal*, March 14, 1903.

⁶ Manson, P., *Tropical Diseases*, 3d Edition, 1903.

Etiology.—*Geographical Distribution.*—Human trypanosomiasis has been known for the last hundred years on the West Coast of Africa, and the disease may be said to extend from the River Gambia to the River Congo. At the present time it does not seem to be a common disease on the Gambia. Dr. Forde, the Principal Medical Officer at Bathurst, reports that, on an average, he only sees about one case a year, and only 6 out of 1,043 natives showed trypanosomes in their blood at Leopoldville. On the Congo, of 1,172 natives, 103 were affected. These included healthy laborers, prisoners, out-patients and patients in hospital. Out of the 103 cases, 57 were recognized as sleeping sickness. These natives were examined for trypanosomes by microscopic examination of a drop of blood from the finger-tip. If we had examined the apparently healthy natives in this way in Uganda probably not more than 1 or 2 would have been detected. It is therefore probable that if a more thorough examination of the blood had been made on the Congo a larger percentage of cases would have been found.

If a map of Africa be examined it will be seen that the basin of the Congo extends more than half across the continent, and that one of the tributary rivers, the Aruwimi, rises near Lake Albert in the northwest of the Uganda Protectorate. At present, the distribution of the disease has not been mapped out completely in the Congo State, but when it is, undoubtedly it will be found to extend far inland. It is therefore not to be wondered at that the disease has crept still further eastward and invaded Uganda. It first broke out in that part of the country lying to the northeast of the great lake, Victoria Nyanza, called Usoga. Dr. Moffat, the Principal Medical Officer in Uganda, is of opinion that the disease was introduced when Emin Pasha's Soudanese, with their wives and followers, numbering some ten thousand, were brought into and settled in Usoga. These natives were brought from the edge of the Congo territory, where in all probability sleeping sickness was endemic. It seems, then, quite probable that some of these natives introduced the disease into Usoga. Be that as it may, the sleeping sickness broke out in that part of the country, according to Dr. Hodges, about the year 1896. It was not recognized, however, till 1901, when the cases became numerous. That this introduction of sleeping sickness from the Congo to Uganda should have taken place in recent years should be no matter for surprise. As Moffat remarks, the recent opening up of Equatorial Africa has led to inter-communication between countries and districts, which, in earlier days, were absolutely cut off from each other. Civilization gives the natives of Uganda peace, and at the same time introduces a disease, which, during the last three years, has killed off a hundred thousand of the population.

Race.—For a long time it was considered that this disease was confined to negroes. Unhappily, this is not so; several Europeans have now succumbed to the disease, as well as the natives of Persia and India. Christy states that the Nubian police in Uganda are practically immune, but this is obviously an error as several of these men were affected and under our observation in Entebbe.

Occupation.—Whatever occupation leads a native to spend much time on the wooded shores of Victoria Nyanza or any river or lake within the sleeping sickness area, is dangerous. Hence, fishermen, canoe-men and

the inhabitants generally of the lake shore are prone to suffer. These people are half naked and spend much of their time trading and gossiping on the shore, 30 to 80 per cent. of them harboring the trypanosomes in their blood, and being constantly bitten by numerous tsetse-flies. Sex, age, food, health or ill-health, have naturally no effect; if the trypanosome is introduced under the skin of the youngest or the healthiest there is no reason to believe that it does not take root and multiply.

Months and Seasons.—As the climate in Central Africa is much the same all the year round it does not appear that the disease is more prevalent at one season than at another.

Description of the Causal Agent—the Trypanosoma Gambiense.—When the blood of a man suffering from human trypanosomiasis or sleeping sickness is examined microscopically, a minute, wriggling, worm-like parasite may sometimes be seen among the red blood corpuscles. It must not be supposed that a casual examination of the blood is all that is required to demonstrate this body. An ordinary blood preparation, taken from the ear or finger, would, in all probability, not show this parasite once in fifty times. As a rule the trypanosomes are so scanty in the peripheral blood that, in order to demonstrate them in every case, a quantity of blood must be examined. In Uganda we examined many cases of sleeping sickness and found the trypanosomes in the peripheral blood of all but one. At that time we had five workers and five microscopes. Ten cubic centimeters of blood were drawn off from a vein of the arm; this was run into test-tubes containing a small quantity of citrate of soda solution in order to prevent coagulation; the blood was then centrifugalized for a quarter of an hour, to throw out the red blood corpuscles; the clear liquid was pipetted off and again centrifugalized for a quarter of an hour. Specimens were taken from the surface of the red blood corpuscles and examined by the five workers. As soon as the moderately clear fluid had been subjected to the fifteen minutes' centrifuging, it was poured off, leaving a small quantity of sediment behind. This sediment was again made into five specimens and examined microscopically. The clear, supernatant fluid was for the third time centrifugalized and the resulting small quantity of sediment again examined. As a rule, it was in the sediment obtained from the third process that we found the trypanosomes most frequently. It will be seen then that five microscopes were employed and frequently fifteen preparations would be examined before a parasite was discovered. In the specimens made from the first two preparations there are too many red blood corpuscles to give a good view; it is only in the third, or perhaps not till the fourth, that the red blood corpuscles have been so completely removed as to leave a clear fluid only containing a few white blood corpuscles; in this fluid the active, living trypanosome is readily picked out under a low power.

The best method of bringing out the various details in the trypanosome is by the use of one of the many Romanowsky staining methods. The method we used in Uganda was that known by the name of Leishman's stain. This is an exceedingly simple stain to use and good results are invariably obtained with little trouble. The following is a description of the method, in Leishman's own words, "I need not recapitulate the somewhat complicated method by which the solid stain is prepared, as those

who wish may refer to my original communication;¹ but there are several points in the preparation of the solution which are of importance to those who have to make this up for themselves. The solvent for the powdered stain is methyl alcohol and it is of the first importance that the right quality of methyl alcohol should be used for the purpose; namely, Merck's methyl alcohol ('pro analysi, acetone free'). Good results are not to be expected if less pure varieties are employed. The powdered stain is dissolved in this alcohol in the proportion of 0.15 per cent., and the following details must be observed in preparing the solution in order to obtain its maximum staining power. The powder should be ground in a clean mortar as finely as possible and the proper proportion of methyl alcohol measured into a convenient vessel; a little of the alcohol is then poured into the mortar, and the grinding continued for some time. After a few minutes' rest, to allow the undissolved particles to sink to the bottom, the upper part of the fluid is poured into a clean bottle, a fresh supply of the alcohol is added and again rubbed up with the remains of the powder. This process is repeated until the whole of the finely divided powder is in this way dissolved in the proper quantity of solvent. This procedure is rendered necessary by the slight solubility of the powder—.15 per cent being nearly a saturated solution—and, if not carried out, or if filtration through filter paper is employed, the resulting solution will be unduly weak and the results obtained with it inferior."

"Thin, even films of blood are made upon *perfectly clean* coverglasses or slides and are allowed to dry in the air or by gentle heat. A few drops of the stain are poured upon the unfixed film and allowed to act for fifteen to thirty seconds, by which time the film will be fixed by the methyl alcohol—previous fixation by most of the methods in general use will prevent chromatin staining. Only enough stain should be used to cover the film with a shallow layer, and care must be taken by moving the slide or coverglass to prevent the stain drying upon any part of the film. At the end of this time double the quantity of distilled water—not more—is added to the stain, and the water and the alcoholic stain are at once thoroughly mixed by shaking, or with the help of a needle held parallel to the surface of the glass and passed backward and forward through the fluid. When the stain is thoroughly mixed with the water the mixture is left on the film for five minutes, by which time an iridescent scum will have formed on the surface and a fine flocculent precipitate will be seen to have formed. This period of five minutes is ample for all ordinary blood work, such as leukocytic counts and the demonstration of malaria parasites, and the stain must now be gently washed off by pouring on the film a little distilled water. When all the precipitate and stain is washed away a little of the water is allowed to rest on the film for half a minute, as this intensifies the brightness of the color-contrasts of the various cells, and advantage may be taken of this moment to glance at the film with the one-sixth inch lens to make sure that the Romanowsky staining is deep enough. The dense nuclei of the polynuclears or lymphocytes form the best index of the depth of staining, and should appear of a deep purplish-red or ruby color. If these are seen to be too light in tint, as may happen

¹ Leishman, Major W. B., R. A. M. C., *British Medical Journal*, September 21, 1902.

with old or bad films, the stain may be re-applied as before until the proper density of nuclear staining is attained."

"Stain trypanosomes for ten to fifteen minutes, controlling the depth of staining by examination under a low power while the film is soaking in water. To bring out all the details of their structure rather deep staining is necessary, and the film may be allowed to soak in water for a little longer than usual. When treated thus, the macronucleus appears red, the micronucleus black, the flagellum red, and the basophile granules black, while the protoplasm of the parasite is colored blue."

FIG. 31.



Fig. 31 represents the trypanosomes in the blood of sleeping sickness cases, magnified 2,000 diameters, and shows the macronucleus in the centre of the body, the micronucleus at the posterior end; the flagellum taking its origin from the micronucleus and, running along the margin of the undulating membrane, becomes free at the anterior extremity. A large vacuole is seen near the micronucleus and dots of chromatin are scattered through the protoplasm. Some writers profess to be able to recognize the various species of trypanosomes by their shape and general appearance. In this way Plimmer makes out that the trypanosome found in Gambia fever, or human trypanosomiasis, is different from that found in sleeping sickness. Without being too dogmatic on this point, the writer's opinion is that it must be very difficult to distinguish between such trypanosomes as *T. evansi*, *T. brucei*, and *T. gambiense* by microscopic examination alone. Koch, on the other hand, refuses to recognize more than one or two species and would group most of the trypanosomes under one specific name.

To Find the Trypanosomes in the Cerebrospinal Fluid.—In the earlier stages of human trypanosomiasis, the trypanosomes are seldom, if ever, found in the cerebrospinal fluid. It is only when the symptoms of sleeping sickness have appeared that they are found with any frequency. In Uganda we examined 40 cases of sleeping sickness by drawing off a small quantity of cerebrospinal fluid and found the trypanosomes in every case. In all the cases the patient was chloroformed as the operation done without an anæsthetic gives rise, evidently, to a good deal of pain, and the native of Uganda was extremely nervous and easily frightened. They take chloroform very easily. Ten to fifteen cubic centimeters of the cerebrospinal fluid are allowed to flow into a test-tube. It is needless to say that if any blood escapes with the cerebrospinal fluid the specimen ought to be rejected. The clear, transparent, water-like fluid is then centrifuged for twenty minutes to half an hour, and the sediment examined in the usual way under a low power. As might be expected, the trypanosomes are seen very readily in the fields of the microscope, there being no red blood corpuscles and few cells of any kind.

The Trypanosomes Found in Enlarged Lymphatic Glands.—One of the earliest manifestations of this disease is an enlargement of the lymphatic glands. It is quite true that among natives going about constantly with bare feet, and their naked limbs exposed to scratches and wounds of every description, it is the rule and not the exception for them to have enlarged femoral glands. But in human trypanosomiasis all the glands are enlarged—the cervical, axillary, inguinal, femoral, etc. Captain Greig, Indian Medical Service, and Lieutenant Gray, Royal Army Medical Corps, made the important observation that the trypanosomes can be demonstrated with great ease in the swollen lymphatic glands, where they seem to be in much greater numbers than in the blood or the cerebrospinal fluid. Greig found that it was only necessary to draw off a drop of fluid by means of a small hypodermic syringe from one of the swollen cervical glands and to place this fluid under the microscope to find the trypanosomes at once or in a comparatively short time. This is a great advance on the older methods of examining the blood and cerebrospinal fluid. It is no exaggeration to say that it took on an average an hour to find the trypanosomes in the blood of a patient, even when there were five microscopes employed. Now, it appears from Greig's report that the cervical lymphatic glands can be examined and the trypanosomes found with great ease in a few minutes.

In What Tissues of the Body can the Trypanosoma Gambiense be Found?—It seems that when the trypanosome is injected under the skin it makes its way by the lymphatic channels and is evidently at first blocked in the lymphatic glands; this causes the swelling of the glands, and, as mentioned above, the trypanosomes are found in much greater numbers in the juice of these glands than in any other of the fluids of the body. From the glands they evidently pass in small numbers into the general circulation, and with it to every part of the body. The living trypanosomes are never found in any of the cells of the tissues but are restricted to the fluids. There can be no doubt that in the first stages of the disease the trypanosomes are not found in the cerebrospinal fluid. In an examination of many apparently healthy natives who had trypanosomes in their blood, trypanosomes were not found in a single case by

lumbar puncture. In the later stage, however, when the symptoms of sleeping sickness supervene, the trypanosomes can as a rule be readily found in every case of the disease in the cerebrospinal fluid.

Mode of Reproduction of the Trypanosoma Gambiense.—As far as is known up to the present this trypanosome only reproduces itself within the human organism by longitudinal division. Other modes of reproduction have been described by various authors, but these at the present time are not sufficiently definite to warrant acceptance. There can be no doubt that the number of trypanosomes varies greatly from time to time in the blood and fluids. Huge numbers of them must perish at times and their dead bodies become dissolved in the blood plasma. It is supposed by some that these dead trypanosomes contain a small quantity of toxin which is thus set free in the blood and gives rise to the proliferation of the lymphatic elements, and to the chronic conditions afterwards found in the brain and tissues.

Life History of Trypanosoma Gambiense outside the Body.—It is evident that as the *Trypanosoma Gambiense* is only found in the blood and lymphatic fluids of the body, it can only leave the body on the escape of these fluids. There is no evidence that the trypanosome escapes from the body by the intestinal or urinary tracts, or by the sweat, salivary or other secretions. When an animal dies of the disease all the parasites disappear rapidly from the tissues on account of commencing putrefaction. If blood is drawn off during life and kept aseptic it only retains its virulence for four days. Blood dried on threads sometimes retains its infectivity for twenty-four hours; at the end of forty-eight hours it is inert. If exposed to a temperature of 40° to 44° C. it is slowly killed; 45° C. is rapidly fatal. The curious observation has been made that trypanosomes, like some bacteria, can be frozen at the temperature of liquid air (-191° C.) for a quarter of an hour and still retain their vitality. There is, therefore, no evidence that the trypanosome is capable of retaining its vitality in external nature under natural conditions for more than a few hours. Under artificial conditions, however, Novy and MacNeal¹ did a remarkable feat in growing various trypanosomes on artificial media. The culture medium they used was ordinary nutrient agar to which had been added defibrinated rabbit's blood. They first succeeded in growing the rat trypanosome in 1903. Later in the same year they also succeeded in cultivating *Trypanosoma Brucei* outside the body. These cultures are, however, by no means so readily obtained as in the case of the rat trypanosome. In this way *Trypanosoma Brucei* has been grown artificially through twenty-three generations, and, so far as the writer knows, is still being grown. Up to the present no one has succeeded in the artificial cultivation of *Trypanosoma Gambiense*, but this will probably be a question of time. It is to be hoped that the cultivation of the various trypanosomes will assist in the identification of species as at present their classification is rapidly

¹ MacNeal, "The life history of *Trypanosoma Lewisi* and *Trypanosoma Brucei*," *Journal of Infectious Diseases*, Vol. 1, No. 4, November 5, 1904, pp. 517-543, Novy and MacNeal, "The cultivation of *Trypanosoma Brucei*," *Journal of the American Medical Association*, November 21, 1903. *Journal of Infectious Diseases*, Vol. I, No. 1, January, 1904, p. 1; MacNeal, "An improved medium for cultivating *Trypanosoma Brucei*," *Sixth Annual Report of The Michigan Academy of Science*.

becoming chaotic. But to return to the question of how the trypanosomes can leave the body of the host. The common way in nature is by the agency of biting flies. It will be interesting then to trace the history of the trypanosome in the interior of one of these flies—the tsetse-fly. *A priori* one would think that the trypanosomes on being taken into the stomach of the tsetse-fly would soon perish¹ on account of the processes of digestion going on. The result of observation, however, shows that the following are the facts as far as have been ascertained: Immediately after feeding, the tube of the proboscis can be seen to be crammed full of red blood corpuscles, among which the trypanosomes can be seen actively wriggling. Up to forty-six hours one can see living trypanosomes and red blood corpuscles in the proboscis. After one hundred and eighteen hours the parasites are still numerous and actively moving about in what remains of the blood in the stomach. After one hundred and forty hours the stomach is empty and no appearance of trypanosomes can be seen. Motionless, apparently dead, trypanosomes are sometimes seen in the contents of the lower intestine, but the result of the injection of the droppings into susceptible animals always remained negative. There was never any sign that the trypanosomes undergo any metamorphosis in the stomach of the fly, such as occur in malaria. In regard to this life of the trypanosome in the stomach of the tsetse-fly, there is some evidence that multiplication may take place, as division forms are seen. In the opinion of the writer, if this takes place, it can only be to a slight extent, and it seems more reasonable to believe that no such multiplication takes place. It seems strange that although the trypanosome remains actively alive for some five days in the fly, we have never been able to infect an animal by means of the bite of the fly for a longer period than two days after feeding. This may be due to the fact that the trypanosome rapidly loses its virulence *in vitro*, and it is probable that this also takes place in the interior of the fly.

How does the Trypanosoma Gambiense Gain Entrance to the Human Organism?—It is difficult to imagine that a delicate blood parasite, incapable of living for any length of time outside the body, can pass from man to man in food, water, or dust, as so many other infectious agents do. When the question came to be asked in Uganda, the old work on nagana in Zululand came to the writer's aid, and a tsetse-fly was at once suspected of being the carrier. At this time it was hardly known that tsetse-flies were found in Uganda, but a short walk along the lake shore soon disposed of that objection. A species of tsetse-fly, afterward identified by Austen as the *Glossina palpalis*, was found to be exceedingly abundant. For months, a few native lads employed to catch these flies, brought three or four hundred daily to the laboratory. This *Glossina palpalis* is very similar to the Zululand species, except that the markings on the upper surface of the abdominal segment are less distinct. Full descriptions of these flies are given in Austen's "Monograph,"² from which the two accompanying figures are taken, the first showing *Glossina palpalis* with artificially outspread wings, the other, *Glossina longipennis*, showing the

¹ Bruce, D., *Tsetse-fly Disease or Nagana in Zululand*, Further Report, 1896, Harrison & Sons, St. Martin's Lane, London.

² Austen, *Monograph of the Tsetse-Flies*, Sold by Longmans & Co., 37, Soho Square, London, B. Quaritch, 15, Piccadilly, London, W.

wings crossed like the blade of a pair of scissors, the usual attitude assumed by this genus.

In Uganda, experiments were made to find out if this fly (*Glossina palpalis*) was capable of carrying infection from the affected to the healthy. Tsetse-flies contained in small muslin-sided cages were fed on sleeping sickness patients and then, after a certain time had elapsed, on healthy monkeys. We secured the same results as were previously obtained in

FIG. 32.

*Glossina palpalis*, Rob. (×33).

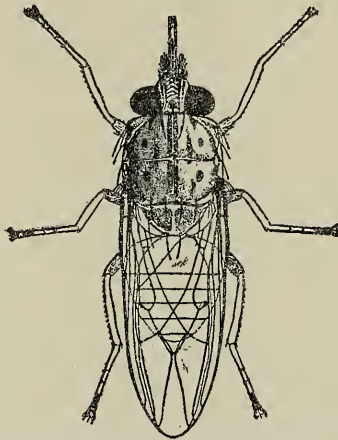
nagana. Flies fed on healthy monkeys, eight, twelve, twenty-four, and forty-eight hours, after having fed on a native suffering from trypanosomiasis, invariably transmitted the disease. After three days the flies failed to transmit it. But this is not the only proof that these flies can carry the infective agent. On the lake shore there was a large native population among whom we had found about one-third to be harboring trypanosomes in their blood. The tsetse-flies caught on this lake shore, brought to the laboratory in cages, and placed straightway on healthy monkeys, gave them the disease in every instance, and furnished a startling proof of the danger of loitering along the lake shore among these infected flies. It is true that the white man runs much less danger than the half-naked native. He is clothed as a rule from head to foot, and resents the presence of a biting fly, whereas the natives lie almost naked in the shade of the dense woods which line the shore of the lake and are little affected by the presence of the tsetse-flies. After these experiments it was held to be proved that the *Glossina palpalis* could convey the trypanosome from the sick to the healthy.

Are other Species of Tsetse-Flies besides Glossina palpalis Capable of Carrying the Infection?—Probably this question must be answered in the

affirmative, as Wiggins, experimenting in British East Africa with *Trypanosoma Gambiense* and species of tsetse-flies other than *palpalis*, succeeded in infecting healthy from affected animals, and Greig and Gray in Uganda found that *Glossina palpalis* could convey the trypanosoma of a disease, probably nagana, which occurred among cattle, as well as that of sleeping sickness.

Do Flies other than the Glossina also Carry the Infection?—The answer to this is, in the writer's opinion, in the negative. Nuttall states that he tried for a long time in England to convey the *Trypanosoma Brucei* by means of the genus of biting flies called *stomoxys*. In no case did he succeed. Greig in Uganda also tried the same experiment and failed. In regard to the *Trypanosoma Brucei* and nagana, there can be little doubt that it is carried by *Glossina* and *Glossina* alone, and the distribution of nagana corresponds with the distribution of the tsetse-fly. So in regard to human trypanosomiasis in Uganda, if the *Trypanosoma*

FIG. 33.



A Tsetse fly (*Glossina longipennis*, Corti, from Somaliland) in resting attitude, showing position of wings. ($\times 3\frac{1}{2}$.)

Gambiense is only carried by the *Glossina* then the distribution of the fly and the disease should correspond. We set ourselves to work out this problem. Collections of all sorts of biting flies were made from all parts of Uganda, and at the same time the distribution of sleeping sickness was carefully enquired into. In the course of a few months several hundred collections of biting flies were examined. These were divided into two categories, those containing tsetse-flies, and those containing other kinds of biting flies but no tsetse. Two maps were taken, one to represent the distribution of *Glossina palpalis*, the other sleeping sickness. On one, over every locality where a tsetse-fly was found, a red dot was placed, and over every spot where other biting flies but no tsetse were found, a black dot was placed. In the same way on the other map red dots represented where sleeping sickness cases were found, black dots where no sleeping sickness cases were found. When these maps were completed it could be seen at a glance that the distribution of *Glossina palpalis* and sleeping

sickness coincided, and therefore we came to the conclusion that human trypanosomiasis is conveyed from the sick to the healthy by the *Glossina palpalis* and by it alone. Austen wrote an account of the biting flies sent to him by us from Uganda, and it can be seen from it that there is no scarcity of genera and species in that country.

Distribution of the Glossina Palpalis in Uganda.—When it became evident that the *Glossina palpalis* was the only carrier of this infection from the sick to the healthy, it was necessary to enquire somewhat closely into its habitat and habits. The results of this showed that this tsetse-fly *palpalis* is only found on the shore of the lake where there is forest. This forest is thick jungle with high trees and dense undergrowth. The fly is never found on open sandy beaches backed by grass plains, even although there may be some scrub near the water's edge. It was never found in the grass of the grassy plains, even although the grass was long and tangled. It was not found by us in banana plantations, and not at any time far from the lake shore. Most of the rivers in Uganda are mere swamps, and up these valleys the fly does not penetrate. The fly is found along the Nile, almost as far north as Gondokoro on the border of the Soudan. It also occurs round Albert Nyanza. In Usoga the fly is seen to occur inland, but what the physical characters of this province are which would account for this have not been learned. Probably, rivers with open water-ways run into this country. It is evidently of the highest importance that the exact distribution of this genus should be made out, as the spread of sleeping sickness to the Albert Nyanza and down the Nile may interfere seriously with the opening up of Upper Egypt.

Animals to which Trypanosoma Gambiense is Pathogenic.—*Trypanosoma Gambiense*, like *Trypanosoma Brucei*, is pathogenic to many species of animals. It is on the whole much more chronic in its action than the latter, the duration of the illness it gives rise to being counted usually by months or even by years. It is curious that *Trypanosoma Gambiense* should include man in its attack, as well as the other animals, whereas *Trypanosoma Brucei*, although as a rule much more rapidly fatal and acute in the lower animals, has never been recorded as having attacked man. Within the limits of this paper it is impossible to enter fully into the course of this disease in the lower animals, but a list of the principle species affected and a short account may be useful:—

Monkeys.—The monkeys we used for inoculation in Uganda were *Macacus rhesus* and a *Cercopithecus*, (sp?). In both species *Trypanosoma Gambiense* gives rise to a chronic and fatal disease resembling human trypanosomiasis. The trypanosomes first appeared in the blood from about the tenth to the twentieth day, were found in smaller or larger numbers every time the blood was examined, and the animals died after an illness lasting from four to twelve months. From our experience the disease is always fatal in monkeys. On *postmortem* examination, the same appearances are found as in man, except that in the fairly rapid cases there is not the characteristic small celled infiltration round the small vessels of the brain which is found constantly in man. In chronic cases, however, this meningo-encephalitis is just as marked in the monkey as in man.

Dogs and Cats.—In Uganda the dogs made unsatisfactory experimental animals, as most of them died of ankylostomiasis before the ex-

periment was finished. Other writers state that dogs die about two months after inoculation, and cats seem to be affected in much the same way as dogs.

Guinea-pigs.—These animals are also susceptible, but in them the disease pursues an extremely chronic course. In Uganda in two guinea-pigs which were inoculated more than once, the trypanosomes only appeared in the blood after twelve and fifteen months respectively. According to Thomas the disease is sometimes fatal.¹ It is probable that sooner or later all the animals die of the infection but this cannot be affirmed at present. *Rabbits.*—Incubation period, according to Laveran and Mesnil, five to fifteen days. Duration from fifty to one hundred and twenty-eight days. *Rats.*—Incubation period four to forty-seven days. Duration from forty-five to three hundred and eighty-eight days (average 85). *Mice.*—Incubation period one to thirty-seven days. Duration from eleven to fourteen days. *Goats.*—One of the goats in Uganda showed *Trypanosoma Gambiense* in the blood about fifteen months after infection. *Sheep, horses, asses and cattle,* are also very refractory, the trypanosomes appearing but rarely in the blood, although the blood may be virulent if injected into susceptible animals.

Effect of Trypanosoma Gambiense on Man—Symptoms—1st Stage—Trypanosomiasis.—When the *Trypanosoma Gambiense* gains entrance to the human organism it begins to multiply and appears in the blood. How long it is before it appears in the general circulation, is, of course, unknown, but in the monkey it usually appears about twenty days after inoculation. The course of the disease is so slow and insidious that months and even years may elapse before any marked signs manifest themselves. As an example of this, in Uganda in March, 1903, we had five natives in Entebbe under constant supervision. In January, 1905, after a period of nearly two years, Captain Greig informed the writer that 2 of these men died of pneumonia in April and May, 1904, respectively. Of the others, 1 appears to be undoubtedly in an early stage of sleeping sickness; he has gradually developed the characteristic signs of the malady and trypanosomes are now always found in his cerebrospinal fluid. The remaining two present some of the features of the disease, but are still able to do their work and have not yet shown trypanosomes in the cerebrospinal fluid. Again in June, 1903, 80 apparently healthy natives from the sleeping sickness area were examined and trypanosomes found in the blood of 23.² Captain Greig now reports that 4 have died of undoubted sleeping sickness, 2 died from pneumonia, 5 are now in an early stage of the disease. No information could be gained concerning 6, and the remainder do not show any symptoms of sleeping sickness. Dr. Wiggins also relates the case of an "Askari" or native policeman, stationed at Fort Ternan in British East Africa for two and a half years before he developed the disease.

All these facts go to show that the first stage of this disease, when the trypanosomes are found in the blood but not in the cerebrospinal fluid,

¹ Thomas and Linton, *A Comparison of the Trypanosomes of Uganda and the Congo Free State*, Liverpool School of Tropical Medicine, Memoir XIII, p. 75, 1904.

² Bruce, Nabarro and Greig, "Further Report on Sleeping Sickness in Uganda," *Royal Society*, No. IV, *Report of the Sleeping Sickness Commission*, Harrison & Sons, St. Martin's Lane, London, 1903.

may be of a very variable duration. If one may be bold enough to put this into definite figures, it may be said that this so-called stage of trypanosoma fever, this first stage of human trypanosomiasis, may last from three months to three years or more. During this time the native is going about at his ordinary vocation. He says he feels perfectly fit and strong. But there is one outward mark which proclaims the disease and that is the presence of enlarged lymphatic glands. This is a disputed point, but in my opinion this enlargement of the lymphatic glands must be looked on as a constant and early feature of the disease. It is not that enlargement of the inguinal or femoral glands should be taken as a sign of human trypanosomiasis; there must be a polyadenitis, and as a matter of routine, the postcervical glands should be examined first. Every case of sleeping sickness examined by us in Uganda showed this glandular enlargement, and according to Greig and Gray,¹ the trypanosomes are readily demonstrated on examining the gland juice. Later it was found that the early cases of trypanosomiasis, the so-called trypanosoma or Gambia fever, also, in every case, presented enlargement of the lymphatic glands, and in these active trypanosomes could readily be found. The natives themselves are alive to the fact, that, when the glands in the neck enlarge, they will, sooner or later, pass into the stage of sleeping sickness, and their custom is then to eat up their live stock, goats, chickens, etc. This enlargement of the cervical glands was used in Uganda to gauge the incidence of the disease in a sleeping sickness area. The result was that in about three-fourths of the population of the islands of Sesse and Kome this symptom was present. As to whether there is any other symptom which can be depended upon to point to the first stage of this disease, is a question which, in my opinion, must be answered in the negative. Some writers state that there is fever from time to time of an irregular type, but if the charts of the men we kept under observation in Uganda be examined it will be seen that they kept absolutely normal for several months. The first stage of this disease may be dismissed then by saying that the blood and lymphatics contain the trypanosomes, and that there is a general enlargement of the lymphatic glands of the body.

2nd Stage—Sleeping Sickness.—Naturally, in a disease so insidious as this it is impossible to say with absolute accuracy when the first stage merges into the second. But a time comes when a slight change in the man's demeanor becomes evident; when he is less inclined to exert himself; he lies about more during the day, and at last his intimates see that he has the first symptoms of the disease. When these are well advanced the expression of the face is sad, heavy, dull-eyed and apathetic, as is well shown in Plate IV, Fig. 1. The body, however, is well nourished, and this is the rule, even up to the time of death, if the patients are well nursed and fed. Complaints of headache or indefinite pains in other parts of the body are often made. The pulse is rapid, shallow and weak, and the heart sounds faint and distant. The breathing usually presents nothing abnormal. The lymphatic glands are generally enlarged, and vary from the size of a pea to that of a bean. There is nothing abnormal about the skin; it may be at times harsh and rough, but usually is smooth

¹Greig and Gray, "Continuation Report of Sleeping Sickness in Uganda," *Reports of Sleeping Sickness Commission*, No. V, Royal Society, Harrison & Sons, St. Martin's Lane, London, 1905.

PLATE IV

FIG. 1



Sleeping Sickness. Second Stage.

FIG. 2



Sleeping Sickness. Shortly before Death.

and sleek, and any eruption is quite the exception. The gait is weak, uncertain and shuffling. There is little strength in the hand grip and the hands when held out are tremulous. Tremors of the tongue are, as a rule, well marked. The voice is weak, indistinct, and monotonous. At this time the temperature is usually irregular, often normal in the morning and rising to 101° or 102° F. in the evenings. During this time the patients in hospital are usually up a great part of the day, sitting in the open air, and to the casual observer show little or no signs of disease. The symptoms gradually increase until after weeks or months the patient is unable to walk, speak or feed himself. He is then altogether confined to his bed, lying in an absolutely lethargic condition all day long. It is at this time that the sick are often neglected by their friends and become much emaciated. The urine and feces are passed involuntarily. During the last two or three weeks the temperature sinks six or seven degrees below the normal, and, the condition gradually deepening, the patient dies in a state of coma.

Plate IV, Fig. 2, represents a case of the emaciated type taken a few days before death.

Principal Symptoms in Detail.—*Nervous System.*—The dull, heavy, listless, expressionless, emotionless physiognomy is a marked feature of this disease. Often when a patient is being examined he stares at a fixed point in a vacant way with eyes wide open. The intelligence and memory seem, as a rule, to remain fairly good. On two or three occasions we meet with cases showing mental excitement, laughing and jabbering all day in a meaningless way. In regard to sleep the usual history is that the patients sleep well at night and a good deal during the day. The condition however, can hardly be called sleep. It is rather a vacant, day-dreaming, apathetic condition in which the patient remains for hours, often with eyes open, staring unmeaningly at the wall. They can easily be roused from this state by touching or speaking to them. The speech is peculiar: weak, slow, tremulous and indistinct, sometimes faint and high-pitched, like a whimpering child. When asked a question some little time elapses before the patient answers; he gives, as it were, a sigh, gathers his wits together, and answers with an evident effort. There is nothing, as a rule, noteworthy about the eyes. There is frequently marked tremor of the tongue, lips, and hands, but the tongue alone may be affected. The muscular nutrition is usually good, but power is diminished as evinced by the grip. Sensibility to touch, temperature, and pain is normal and the muscular sense is little impaired. In regard to the reflexes, as a rule there is no abnormality. Sometimes, in the early stages, the knee-, elbow-, and wrist-jerks are increased; but in advanced cases the knee-jerks are often diminished and ankle clonus is in rare cases present to a slight extent.

Alimentary System.—There is little or nothing to be noted here. The appetite is usually good, even in fairly advanced cases. The tongue is moist, flabby, and furred. Inspection of the abdomen seldom reveals anything. There is, as a rule, no enlargement of the liver and the spleen is rarely palpable. The bowels tend to be constipated and aperients are often required. When the patient is bed-ridden, unless care is taken, the colon becomes full of hard scybala.

Circulatory System.—This is more important from a diagnostic point of view, as the heart and pulse tend to become affected early in the dis-

ease. In regard to the heart no patient at any time made any complaint as to pain or palpitation. On examining the cardiac area the apex beat was found usually either very weak or imperceptible, but nothing else abnormal could, as a rule, be made out. On auscultation the heart sounds are weak but regular, and there is, in the great majority of cases, no bruit. The pulse is usually accelerated. It has a rate, as a rule, of from about ninety to one hundred, with a low tension, a small size, easily compressible and regular rhythm.

Respiratory System.—In all the cases of sleeping sickness examined by us in Uganda, the lungs presented nothing abnormal. The breathing is naturally somewhat increased in frequency when there is fever, and there is some congestion of the bases in the last few days of life. Pneumonia seems to supervene more frequently in sleeping sickness cases than among the healthy. Dr. Cooke, Kampala, observes that the mortality among the natives from pneumonia has greatly risen since the occurrence of the sleeping sickness epidemic.

Urinary System.—There is also, as a rule, nothing noteworthy to be found in this system.

Cutaneous System.—Sometimes the skin is harsh and rough, and the papillæ prominent, especially over the legs and arms, but in the great majority of cases there is nothing abnormal. In one case we noticed an œdematous swelling over the shin, but, as a rule, swelling, puffiness and eruptions are conspicuous by their absence.

Lymphatic System.—In every case the superficial lymphatic glands are slightly enlarged, varying, as a rule, from the size of a pea to a bean. They are fairly soft and painless, but in a few cases in the last stages they become inflamed, tender, and break down. This is probably due to a terminal bacterial invasion and not to the trypanosomes. This polyadenitis is considered to be one of the most characteristic signs of this disease and is only found among natives inhabiting the sleeping sickness area. It may then be accepted as the most marked symptom of the disease.

Hæmopoietic System.—Anæmia is not a feature of sleeping sickness; in uncomplicated cases no diminution of the number of the red blood corpuscles, or percentage of hæmoglobin, takes place. Greig and Gray state that “toward the end in a certain proportion of cases the number of red cells, the percentage of hæmoglobin and the specific gravity, rise. These cases did not present any signs of cyanosis.”

Low and Castellani, on the other hand, say that anæmia in varying amount is constant, the average number of the red blood corpuscles per cubic millimeter being 3,500,000 or thereabout, and that the hæmoglobin is generally reduced proportionately.

In regard to the leukocytes Greig and Gray state that a lymphocytosis occurs in all cases. They write that “enlargement of lymphatic glands being a constant feature in sleeping sickness, it is a matter of importance to determine whether the lymphocytes in the blood show an increase in numbers. This point is of interest, further, because the most constant lesion found in the nervous system of sleeping sickness cases is an accumulation of cells of this nature in the perivascular lymph spaces.” Greig and Gray also made the interesting observation that all the cells found in the cerebrospinal fluid were lymphocytes and that they increased in

number from 23 per Cc. in the early stage, to 730 per Cc. in the fully developed disease. The total number of leukocytes per Ccm. remains fairly normal, lying, as a rule, between 7,000 and 10,000, sometimes rising to 15,000 and 20,000. Greig and Gray's averages work out for the red blood corpuscles at 4,707,000, white blood corpuscles 11,000, eosinophiles 5 per cent., polynuclears 39 per cent., large mononuclears 12 per cent., and lymphocytes 38 per cent. Needless to say, among natives who all suffer more or less from helminthiasis there is often found a varying eosinophilia.

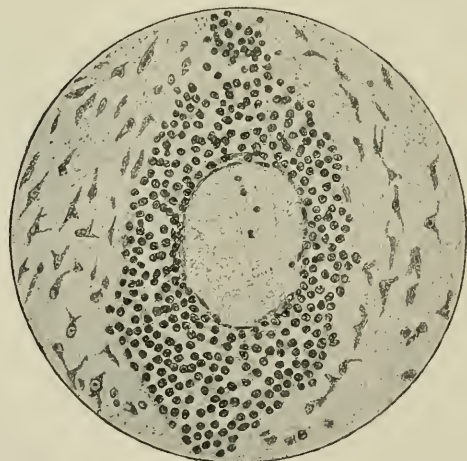
The Temperature Curve.—There is nothing very marked about the temperature curve in human trypanosomiasis. In the early stage, when the trypanosomes are found in the blood and before symptoms of sleeping sickness appear, the temperature remains normal. The cases under observation in Entebbe remained without any rise of temperature for six or seven months, and it is impossible to say how long they harbored the parasite before coming under observation. When symptoms of sleeping sickness appear, the temperature, as a rule, becomes irregular, rising to 101° F. or 102° F. in the evening and sinking to normal or slightly below normal in the morning. But it must be admitted that cases occur with the temperature fairly normal throughout the disease, although there is always a certain irregularity. High temperatures may be said never to occur—103° F. being a rare exception, and these are probably often due to an attack of malaria. There is one characteristic about the curve which is fairly constant: about a fortnight before death the temperature runs rapidly down 94°, 93°, and 92° F., and remains so until death. When the temperature becomes subnormal morning and evening, the patient will probably die within a fortnight. To recapitulate then, the few cases of human trypanosomiasis we have been able to follow, up to the present, show a normal temperature for six or seven months. During this time the trypanosomes are constantly found in the blood. Then the temperature becomes slightly irregular, the patient becomes heavier and duller in his demeanor, the trypanosomes begin to appear in the cerebrospinal fluid, and the stage of sleeping sickness may be said to be entered. The temperature remains irregular with two or three degrees of fever in the evening, until a fortnight before death when it becomes subnormal, running down to 93° and 92° F.

Special Pathology.—There is little of special interest to be noted at the *postmortem* examination of an uncomplicated case of human trypanosomiasis. The body is usually well nourished, but may be extremely emaciated. There are usually bed-sores present, or at least commencing bed-sores. The effect of the long chronic disease renders the heart muscle flabby and the liver fatty. The lungs and kidneys present nothing abnormal, except the congestion incident to a failing circulation. In a malarious region, naturally, the spleen is usually somewhat enlarged, pigmented and tough. Of course, the patient may die of some intercurrent malady, such as pneumonia, which is common enough, and the signs of the disease will be present. But it may be safely said that, except for the constant presence of general enlargement of the lymphatic glands, there is nothing in the naked-eye appearances to proclaim human trypanosomiasis. The lymphatic glands, both superficial and deep, are enlarged. The superficial usually vary in size from a pea to a large bean, and the

deep run somewhat larger. Sometimes they increase very much in size, and on section are found to be caseous or to contain collections of pus. This is probably due to some terminal bacterial invasion and not to the trypanosomes. But when one comes to examine the brain there is a divergence from the normal and a pathological picture which is fairly regular. On removing the calvarium, as a rule, a good deal of fluid escapes. The dura mater is not adherent, and, usually, presents nothing abnormal. On reflecting it the convolutions on the surface of the brain are found to be flattened, and the sulci filled with opaque-looking sub-arachnoid fluid, giving a ground-glass appearance. The vessels on the surface are injected. On section the brain appears normal, but the lateral ventricles are dilated and contain an excess of fluid. This is all that can be seen on exposing the surface of the brain of an ordinary uncomplicated case of sleeping sickness, but which, in my opinion, constitute an appearance fairly characteristic of sleeping sickness. A certain percentage of the cases present much more acute signs of disease. These are the cases in which a terminal bacterial infection has taken place, and the brain may then present all the appearances of acute or purulent meningitis.

Microscopic Examination of the Tissues.—It is to Mott we owe our knowledge of the pathological histology of sleeping sickness. He states that a definite characteristic appearance is found in sections of the brain, which is found in no other disease. He is able to pick out with certainty from a number of sections of brains of various nervous disorders, such as tabes and general paralysis, those cut from sleeping sickness cases. This is a condition of meningo-encephalomyelitis. Throughout the whole central system, but especially in the medulla, and at the base of the brain,

FIG. 34.



sections show the pia arachnoid to be infiltrated with mononuclear leukocytes; the inflammation can be traced along the bloodvessels and septa into the substance of the nervous system. The perivascular lymphatics around both large and small vessels are crowded with these lymphocytes.

Fig. 34 is taken from his paper and shows this collection of lymphocytes in the perivascular spaces. But this lymphocytic accumulation in the perivascular spaces of the brain and spinal cord is not restricted to the nervous system, but is found all over the body. We have seen that there is an increase of the lymphocytes in the blood and that the lymphatic glands are enlarged and show a proliferation of these cells. In short, throughout the body and especially in those tissues and organs rich in lymphatics, such as the intestine, this proliferation and accumulation can be seen. Human trypanosomiasis is essentially then a disease of the lymphatic system, and the irritation and proliferation of the lymphocytes is probably due to a toxin secreted by, or contained in, the bodies of the trypanosomes. The characteristic symptoms of the disease are no doubt due to the accumulation of these lymphocytes in the perivascular spaces of the brain, compressing the arteries and so interfering with the normal nutrition of the brain cells. The progressive weakness of the body, the tremulous condition of the muscles, the feeble rapid pulse, the weak voice, and uncertain gait, the rise of temperature, would all be accounted for by this obstruction or interference with the circulation, giving rise to degenerative changes in the nerve cells, and proliferation of the neuroglia.

Terminal Bacterial Invasion.—Some writers are of the opinion that the bacteria, chiefly cocci, found frequently in the tissues of sleeping sickness cases after death, may be an important etiological factor in the disease. It is necessary then to say a few words on this subject. The Portuguese Commission described a diplo-streptococcus which they found in the cerebrospinal fluid after death, and during life by lumbar puncture. Castellani in 39 cases grew streptococci from the blood of the heart in 32 and from fluid taken from the lateral ventricles in 30. During life, he found his streptococcus very rarely and only in the last stages of the disease. He examined the cerebrospinal fluid obtained by lumbar puncture in 28 patients; in 5 he had positive results, but only when the examination was made a few hours before death, with the exception of 1 case in which he found it several days before death. Greig and Gray also made a number of observations by making cultures from the glands, blood, and cerebrospinal fluid. They say that "the result of these observations showed that a number remained cases of pure trypanosoma infection to the end; the cultures made from the glands, blood, and cerebrospinal fluid remained sterile. On the other hand, in a proportion of cases, an invasion, chiefly by diplo-streptococcus, did occur but, by the results of the examination at different stages of the disease, it was possible to locate it to the final stage, when the patient was practically moribund. These cases at this stage of the disease have invariably numerous foci of suppuration on the hands and feet due to jiggers; also there is frequently before death a purulent discharge from the gums; and their vitality and resisting power is a negative quantity." The writer's opinion of the *role* played by the diplo-streptococcus has always been that it is merely a terminal infection in the last days, when the patient is practically dead. At the same time it must sometimes hasten the end, and the cases of pneumonia, acute and purulent meningitis, which are often met with at autopsy of cases of sleeping sickness are due to bacterial invasions of the pneumococcus, the diplo-streptococcus, and other organisms. In nagana there is also frequently found a streptococcal terminal infection.

The writer does not believe that the diplo-streptococcus plays any more important part, and it may be relegated to the lumber room to join the *Filaria Perstans*, *Strongyloides*, *Ankylostoma*, and the various bacteria which have been described at various times as the cause of sleeping sickness.

Diagnosis.—From the description of the disease given above, it will be seen that it is no easy matter to diagnose human trypanosomiasis in the early stages. If a case were met with in America or England a history of the patient having lived in Africa in the endemic area within the last four to five years would give a clue: then, in all probability, at the time the patient sought medical advice the temperature would be found to be irregular, with an evening rise of one or two degrees; the pulse also would most likely be suspicious, being quicker than usual and with low tension. The examination of the blood would show a lymphocytic leukocytosis, which would help to exclude some other diseases; and, lastly, a drop of gland juice, removed by a hypodermic needle from a cervical gland, would show *Trypanosoma Gambiense*, and so definitely settle the diagnosis. In more advanced cases the peculiar apathetic physiognomy, the pulse, the temperature curve, the tremors of the tongue and hands, the peculiar speech and weak shuffling gait, ought to form a picture which cannot be mistaken for any other disease. But the one unmistakable mark of the disease is the presence of the *Trypanosoma Gambiense* in the lymphatic glands, blood, or cerebrospinal fluid, and no medical man should rest content with a diagnosis which does not include the demonstration of the parasite.

Prognosis.—Every case of human trypanosomiasis which shows symptoms of sleeping sickness dies sooner or later. It is an absolutely fatal disease. The question has arisen as to whether any of the natives with trypanosomes in their blood are able to kill the parasite off before organic changes in the tissues have been set up, and so establish an immunity. This question cannot yet be answered with certainty. Greig and Gray remark on this point, "In following the after history of cases of trypanosoma fever we have arrived at these conclusions: (1) that many of them terminate fatally as sleeping sickness cases, which may be regarded as the usual mode of termination; (2) that a certain number die of intercurrent affections; *e.g.*, pneumonia; (3) that a certain proportion remain well for long periods, indicating that a tolerance toward the parasite has been obtained. It may be said that some of the cases may become in time sufficiently immune to destroy the parasite. The evidence collected so far suggests that this is the case." The writer agrees with Greig and Gray in everything except the last sentence but it is debatable as to whether the evidence does any such thing. It is of course, a very important point, but we must wait for more knowledge. Of the 5 cases of human trypanosomiasis in natives¹ kept under observation since March, 1903, 2 have died of pneumonia, 1 shows undoubted symptoms of sleeping sickness, and the remaining 2 premonitory symptoms. Another case, a European brought under observation at the same time, came to me at the beginning of 1905 with swollen glands, trypanosomes in his blood,

¹ Bruce and Nabarro, "Progress Report on Sleeping Sickness in Uganda," *Royal Society, No. I. Report of the Sleeping Sickness Commission*, 1903, Harrison & Sons, St. Martin's Lane, London.

complaining of want of energy, and, in my opinion, in an early stage of sleeping sickness. He died afterward of undoubted sleeping sickness. Of the 23 healthy natives with trypanosomes in their blood in 1903, Greig reports at the end of 1904, that "it has been ascertained that since that date 3 have died of undoubted sleeping sickness; 1 ran away from his shamba and was reported to have died of sleeping sickness; 2 died from pneumonia (1 was almost certainly in an early stage of sleeping sickness); 5 are now in an early stage of sleeping sickness; no information has been obtained in 6 cases. The remainder, 6, do not as yet present definite signs of sleeping sickness." There is still time for these 6 to develop symptoms. The incubation period may, as stated above, be three years or more. The evidence rather goes to show that all cases of human trypanosomiasis go on to sleeping sickness and death. Further knowledge is required before the question can be answered dogmatically.

Treatment.—It may be stated at the outset, that up to the present, medical treatment has failed to do more than prolong life. Arsenic has more influence on the trypanosome than any other drug. Horses, donkeys, and cattle suffering from nagana received 12 to 20 grains of arsenic daily. The result was, that in a few days, the parasite disappeared altogether from the blood, and remained out of it for a long time—from one to five or six months. In every case, however, sooner or later, the hæmatozoa crept back into the blood, increased in numbers, and finally killed the animal. In no case was a cure effected. In the most successful case death was delayed for nearly a year. In human trypanosomiasis the same thing seems to occur. The writer has no experience of arsenic in human trypanosomiasis. Low and Castellani say that "iron, arsenic, and quinine, especially in cases complicated with malaria, produced a distinct but temporary improvement." Manson¹ treated his case with arsenic in various forms, both by the mouth and hypodermically; also with methylene blue. The patient died after two years, of sleeping sickness. The Liverpool School of Tropical Medicine states that a "variety of drugs have been used with more or less success; up to the present arsenic and trypanroth, an aniline dye introduced by Ehrlich and Shiga, appear to be most useful; the parasite disappears for a time from the blood, and the life of the animal is prolonged, but with neither of the drugs is a cure obtained." Greig and Gray report several experiments with arsenic. They gave 10, 15 and 20 milligrams of arsenious acid daily. They write that "the effect of arsenic on the trypanosomes in the blood of patients in the early stage of the disease has been observed. The action is somewhat remarkable. The parasite disappears first from the peripheral blood and, at a later date, from the lymphatic glands. After an interval of varying length the parasites will reappear in the blood temporarily and then again disappear, but have not so far returned to the glands. This reappearance of the trypanosomes in the blood and their final disappearance suggests that arsenic acts in two ways: (1) by actually destroying the trypanosomes, and; (2) the trypanosomes so destroyed actively immunize the individual, the effect of this not being apparent till later." As none of these cases have been under observation for more than five months it is, in the writer's opinion, too early to

¹Manson, "Sleeping Sickness and Trypanosomiasis in a European," *British Medical Journal*, December 5, 1903.

generalize; in nagana, it will be remembered, the parasite sooner or later reappeared in the blood and caused the death of the animal. Greig and Gray are also experimenting with trypanroth. Concerning the latter drug Laveran and Mesnil state that they have had no success with it in the case of rats infected with *Trypanosoma Gambiense*. In some of the trypanosome diseases, such as nagana and surra, every conceivable drug has been tried. All the sera have likewise been used. Toxins and cultures of living bacteria of many pathogenic organisms, as well as blood parasites, have also been found useless. In short, everything likely to effect a cure by interfering with the well-being of the trypanosome has been tried, but not a single case of recovery has occurred. At present, then, there is no reasonable hope of a curative agent being found, and preventive treatment seems equally unreachable. Laveran¹ in a later note records the results of his observations on the action of arsenic and trypanroth on the *Trypanosoma Gambiense* in rats and dogs. The method which Laveran adopts for the administration of the drugs is to inject the infected animal with arsenious acid and after an interval of forty-eight hours with trypanroth. He thinks that this treatment carried out three times at intervals of eight days is sufficient to cure the disease in rats. Two rats infected with *Trypanosoma Gambiense* on October 17, 1904, and treated in this way were, in his opinion, cured, the trypanosomes having been absent from the blood for ninety-one days. For dogs he considers that a dose of 1.5 mg. of arsenic per kilo should not be exceeded. For a dog of ten to twelve kilos, he recommends a dose of 14 to 16 milligrams and 30 to 40 centigrams of trypanroth. Plimmer tells us that his rats infected with the trypanosome of sleeping sickness lived for a year without showing any symptoms of disease and without the trypanosomes appearing in their blood. It is evident then that we must wait longer before any results of treatment can be accepted. That a substance could be found with the power of destroying the *Trypanosoma Gambiense* in the tissues of man is "a consummation devoutly to be hoped." Prof. P. Ehrlich is investigating the subject with a view to this and the members of the Sleeping Sickness Commission now in Uganda are testing these drugs on cases of human trypanosomiasis in the earliest stage. Some years must probably elapse before the result of these experiments can become known, but they will be looked forward to with great interest.

Prophylaxis.—Since we have found that at present there is no cure for this disease, we must consider what means may be devised for its prevention. There are three factors to be considered; the human host, the parasite, and the tsetse-fly. If this were a disease affecting a species of the lower animals it is evident that the slaughter of all those with parasites in their blood would in all probability nip an epidemic in the bud. The neglect to take promptly this stamping out measure led to disaster in Mauritius and the Philippines, when surra was introduced into these islands. But we are dealing with man. We have seen that the disease only spreads by means of the tsetse-fly, and in its absence there can be no infection. Is it possible to destroy these flies? They are found in great numbers all round the lake shore, where there is dense forest. There does not seem at present any means by which such insects could be got

¹ *Comptes rendus des seances de l'Academie des Sciences*, CXIV, p. 287, Séance du 30 Janvier, 1905.

rid of. The dense jungle can hardly be entered except by the infrequent native paths. The vegetation is too green and damp to burn. It is possible that, if the life-history of the fly were more fully known, some way of getting at it might be devised. At present the destruction of the carrier as a means of prevention must be reckoned impossible. If the Baganda were an intelligent, civilized race it might be possible to get them to migrate out of the sleeping sickness area, and this is what the intelligent among them do, but the great mass of them are half-naked, ignorant savages, who would rather die than desert their shambas. Again, if any big scheme of migration was attempted, it would be important that the district selected should be first carefully examined for any species of tsetse-fly. We have found that the trypanosomes can be carried by more than one species. It would, therefore, be dangerous to allow of any movement of natives from the sleeping sickness area into, let us say, the eastern parts of British East Africa, where more than one species of tsetse is found. But from what we have learned of the etiology of the disease the method of escaping from it is easy in the extreme. Just as no one would expose his horses or cattle to the danger of passing through a nagana "Fly belt," if he could possibly help it, so no one should expose himself to the danger of living in a sleeping sickness area. If it is necessary to have a settlement near the lake shore much can be done to render it habitable by cutting down the jungle in the vicinity and bringing the ground, if possible, under cultivation.

CHAPTER XXII.

AMŒBIC DYSENTERY.

By RICHARD P. STRONG, M. D.

Synonyms.—Amœbic colitis, amœbic enteritis, amœbiasis.

Definition.—An infectious disease characterized by a variable mode of onset, a course of great irregularity, intestinal disturbances consisting chiefly of intermittent attacks of diarrhœa and constipation, abdominal pain, and the presence of amœbæ, and sometimes of mucus and blood in the dejecta. Besides man, in the tropics smaller monkeys and orang-outangs are attacked.

Historical Note.—While dysentery probably existed in the earliest times, since in the most ancient writing upon medicine, the papyrus Ebers, references are made to it and even in the time of Hippocrates it was regarded as an independent malady, the suggestion of the existence and the first step toward the differentiation of a variety of amœbic origin may be said to date back not earlier than 1859, in which year Lambl called attention to the presence of rhizopoda in the intestinal mucus of a child who had died from enteritis.

This was confirmed in 1875 by Lösch, who found amœbæ in the dejecta during life and in the intestinal lesions at autopsy of a case of chronic dysentery. Lösch gave a careful description of the parasite, which he named *Amœba coli*, and was able by rectal injections of the fæces which contained living amœbæ, to produce dysentery and ulcerations in the lower portion of the large intestine of a dog. Lewis and Cunningham, in 1870 and 1881, on the other hand, found these organisms in cholera stools, as well as in those of individuals suffering from other diseases, and even in the dejecta of healthy persons. They inclined to the belief that they bore no causal relation to intestinal disease. Grassi, Sonsino, Normand, Perroncito, Calandruccio, Blanchard, Koch, and others, likewise observed amœbæ in the stools of those suffering with intestinal disturbances, but Grassi and Perroncito also ascribed no pathogenic properties to these parasites. Koch, however, demonstrated amœbæ in sections of the intestine of those who had died of ulcerative dysentery.

The question of the significance of amœbæ in intestinal disease was uncertain until 1886, when Kartulis published the results of his investigations upon over 150 cases of Egyptian dysentery. Amœbæ were found in the stools of every one of these. In 30 control patients suffering with other diseases he found no amœbæ. Kartulis thoroughly convinced himself that this parasite was the cause of tropical dysentery and reported in his later papers his study of over 500 cases. He also in 1887 found the parasite in cases of dysenteric abscess of the liver. Halava in the same year, in Prague, found amœbæ in 60 instances of partly endemic

and partly sporadic forms of the disease. He experimented upon animals, injecting fæces containing amœbæ into the rectum, and obtained positive results with both dogs and cats.

In Baltimore in 1890, Osler discovered amœbæ in the contents of a liver abscess and in the stools of a patient who was suffering with chronic dysentery, which he had contracted in Panama. Other cases in which amœbæ were found in the stools were then reported in the United States by Musser, Stengel, and Dock. In 1891 Councilman and Lafleur published a complete study of 15 cases from Osler's wards. They described histological peculiarities by which this form of flux differs from other types, and concluded that amœbic dysentery should be regarded etiologically, clinically and anatomically as a distinct disease. It is to their important monograph that we owe much of our present knowledge.

In 1894, Kruse and Pasquale by their extensive studies in Egypt did much towards confirming our belief in the existence of amœbic dysentery as a separate disease with a specific etiology; and Harris, in 1898, by his investigations also added important data in the differentiation of the malady in America. In 1900, the writer showed that the prevailing dysenteries of the Philippine Islands could be divided into two distinct forms, one of which owed its origin to a variety of amœba (*Amœba dysenteriae*), and the other to a species of bacterium (*Bacillus dysenteriae*). Leonard Rogers, in 1902 and 1903, increased our knowledge of the disease as a separate infection in India, where its existence had previously been frequently denied, and showed clearly its association in that country with liver abscess.

These investigations have convinced many of us of the existence of a separate form of dysentery of amœbic origin, and from them and from other experimental studies it seems that we are justified in regarding it as a distinct form of intestinal disease to be distinguished from other varieties of dysentery. However, there is still much objection to this, and it is opposed by a number of authors who have had a wide personal experience in tropical intestinal affections.

Etiology.—Distribution and General Prevalence.—While the disease is widely prevalent and occurs sporadically in many subtropical and temperate countries, in tropical ones it finds its endemic home and is indeed the usual form of dysentery encountered. It is particularly prevalent in the Philippine Islands, India, and Egypt, and not uncommon in South America, particularly in Brazil, and in the Southern United States; sporadic cases are found from time to time in New England, and an occasional case is encountered in the Eastern, Central, and Western States. In the Eastern Hemisphere sporadic cases have occurred, particularly in Russia, Germany, Austria, Italy, and Greece. In temperate climates the disease is rarely epidemic, but occasional outbreaks of moderate size have occurred, such as reported by Jäger, in the German Army, in 1901, in East Prussia.

Relative Incidence in the Philippine Islands.—In 1899–1900 an epidemic of bacillary dysentery occurred in the Philippine Islands, and in a series of 147 fatal cases of both this and of the amœbic form of the disease, 67 per cent. belonged to the latter variety. Of the dysentery cases in Manila during the past two years, over 80 per cent. have been amœbic,

and nearly 90 per cent. of our fatal cases of dysentery have shown at necropsy lesions of this form. The disease is by far the most prevalent one in the Philippine Islands among white people. At the Government Civil Hospital in Manila the records kindly furnished by Dr. G. B. Cook, for the summer months of the year 1904, show that over 30 per cent. of all the white patients admitted had amœbic dysentery.

Meteorological conditions have considerable influence upon the prevalence of the disease. In the Philippine Islands by far the greatest number of cases is recognized between June and September, the largest number appearing after the heavy rains have begun. During the year 1904, after the great flood in Manila in July, the disease became almost epidemic, and the number of cases enormously increased. Harris states that the onset of the malady in the United States is almost invariably in the summer months, May, June, July, and August. Lafleur called attention to the fact that the disease is observed most frequently in districts approaching the sea-level, namely, the shores of the Chesapeake Bay, the Gulf of Mexico, and the Mississippi Valley. This is true also in the Philippine Islands, where near the sea coast and in the low lands the disease is very prevalent, while in the mountains, particularly in Benguet, Luzon, which has an altitude of over 4,000 feet and in which place many of the springs which furnish drinking water contain plentiful numbers of amœbæ undistinguishable from those observed in the water-supply of Manila, the disease, although occasionally encountered, is very rare.

Sex.—All observers agree that the disease is much more prevalent in males. Harris states that it seems to occur in males about three times as frequently as in females. In Futcher's series of 119 cases at the Johns Hopkins Hospital, there were 108 males and 11 females. In the Philippine Islands the disease occurs also more frequently in males. In the Government Civil Hospital of 401 cases, the ratio of males to females is as 4.1 to 1. In 200 personal cases only 23 have been in females. Undoubtedly in the tropics men are more frequently exposed to infection than women on account of their more active life.

Age.—In Futcher's series the greatest number of cases occurred between the ages of twenty-one and thirty years. Of the writer's, 149 among 200 were in the third and fourth decade; only 4 cases occurred in the second. The disease is common in children under ten years of age. Futcher calls attention to 11 such cases. Musgrave has encountered 21 with 1 death in a series of 100, and the writer met with 18. Harris reports 4 cases out of 35, and many other observers have also encountered the disease in young children.

Race.—In the Philippine Islands the white race is much more susceptible than the Malay. The natives, by reason of their mode of life and condition of their drinking water, are constantly exposed to infection, yet they do not suffer nearly so often from it as Americans and Europeans. At the Government Civil Hospital the ratio of white to native patients has been as 2.5 to 1, while the ratio of amœbic dysentery in the two races has been as 9 to 1. Futcher and Harris found that in the United States blacks were somewhat less frequently attacked than whites.

Unhygienic Influences.—Harris states that amœbic dysentery is an affection preëminently of the poor, and is almost always associated with

filth, bad hygienic surroundings and lack of proper food. This, however, does not hold good in the tropics, and in the Philippine Islands all classes are likely to be attacked who do not take continuous and extraordinary precautions in regard to their drinking water. Susceptibility, however, seems to depend considerably in some cases upon the general physical condition of the individual, although sometimes apparently perfectly healthy and robust persons are attacked.

The Amœbæ of the Human Intestine.—These organisms are classed under the rhizopoda of the protozoa. They are unicellular parasites possessing an endosarc and ectosarc which can readily be distinguished when the organism is in motion. The endosarc is granular, and usually encloses several vacuoles of variable size. The ectosarc is clear and more hyaline in appearance. When seen in the fæces they frequently contain red blood corpuscles, the larger forms sometimes enclosing as many as twenty. Pigment granules and bacteria have also been observed in the endosarc.

The parasite moves by means of pseudopodia; blunt processes consisting of the ectosarc are first protruded and into these protrusions the protoplasm of the endosarc appears to flow. The organism is capable of changing not only its shape but also its position and so moves about. It possesses a nucleus which may sometimes be observed in the living forms but which can be more clearly seen in colored preparations. It is usually placed eccentrically in the endosarc and contains a nucleolus. The most satisfactory stain for bringing out the structure of the parasite, in preparations from the stools, has been shown by Woolley to be Borrell's blue. In tissues the thionin stain is more satisfactory for differentiation, and for distinguishing the amœbæ from mast cells. Musgrave recommends Wright's modification of Romanowski's method as most satisfactory for staining permanent preparations of the parasite from cultures, the technique employed being the same as recommended by Wright in staining blood films. The amœbæ multiply by binary fission and by sporulation.

The diameter of the organisms found in the human stools has been variously estimated at from 10 to 50 μ . While they may vary greatly in size in different cases, in the same one they are usually of a fairly uniform diameter. Sometimes in stools that have remained standing for some time, the amœbæ become encysted. They then appear to be surrounded by a coating of two layers, and it is sometimes almost impossible to differentiate them morphologically from other substances. The outer layer of the cyst frequently presents a warty appearance.

Biological Properties.—It is doubtful if amœbæ have been grown artificially in pure culture free from bacteria, though numerous attempts have been made to accomplish this since the reported successful results of Kartulis in 1885. He used a straw decoction as a medium, and thought that he had obtained a pure growth of the parasites from an abscess of the liver which was free from bacteria. In 1895, Celli and Fiocca claimed to have obtained, after great difficulty, amœbæ in pure cultures upon an alkaline media containing *fucus crispus*. However, the organism did not reproduce in transplants. In 1898, Tsujitani reported the pure development of encysted cultures of amœbæ. He took old cultures of a favorable symbiotic organism, heated them for an hour at 60° C., and then

plated to see if all the organisms were dead. These dead cultures were then inoculated with encysted amœbæ and development occurred, though not so luxuriantly as with living bacteria.

However, while the parasites have not been successfully cultivated free from microorganisms, single species have been grown with pure cultures of bacteria by many workers. Musgrave recommends for the cultivation of amœbæ with bacteria, a medium composed of agar 20 grams, sodium chloride and extract of beef each .3 to .5 grams, prepared as ordinary bacterial agar and with a final reaction of 1 per cent. alkaline to phenolphthalein. The cultivation of amœbæ from the stools, according to him, is frequently more difficult than of those found in water. It is necessary that the proper bacteria should be present in the culture in order to obtain a growth of the protozoa. He was unable to cultivate amœbæ which contained red blood cells, as these seemed not to reproduce. Lesage recommends for cultivation ordinary gelatin that has been thoroughly washed with distilled water, and then sterilized.

Behavior Towards Physical Conditions and Chemical Substances.—While most observers have remarked that amœbæ usually lose their motility in the stools at or below 75° F., Musgrave and Clegg have not found this to be the case either in the stools or in cultures. Craig asserts that a freezing temperature kills amœbæ almost instantly. Tuttle goes so far as to say that the behavior of amœbæ found in dysentery differs greatly from that of those found in fresh water when exposed to heat or cold, and that it is this alone which positively distinguishes the two. The latter remain motile at high or low degrees, while the former are viable only at temperatures near that of the body. He states that a temperature of 70° F. is fatal to the motility and life of the dysenteric amœbæ. However, Kruse and Pasquale found by employing a dysenteric stool containing amœbæ which had first been frozen and then subsequently thawed and injected into the rectum of a cat, that a typical dysentery followed and that at necropsy the mucosa of the large intestine was swollen and reddened and covered with mucus in which living amœbæ were found. Harris found that these organisms were not killed in any reasonable length of time by lowering the temperature of the fluid in which they were contained to 0° C. Musgrave, moreover, has shown that *extreme* cold sometimes does not destroy this parasite. An encysted culture of an amœba isolated from a dysenteric stool was placed in cold storage at - 12° C., for forty-five days; at the end of this time a transplant gave a fresh growth of the amœbæ. The same experiment was repeated with another strain of the organism isolated from a dysenteric stool and with one isolated from water, but with neither of these did any growth result. A temperature of 60° C. maintained for one hour usually suffices to kill encysted cultures, though considerable variation has been noted in the temperature necessary to destroy different strains.

The action of various *chemical substances* upon amœbæ has received attention for a long time. Harris found that amœbæ (in the stools) were not seemingly affected by saturated solutions of quinine sulphate or boric acid, though 1 to 300 solution of quinine bisulphate invariably killed them within ten minutes. They were destroyed by weak solutions of hydrogen dioxide, potassium permanganate, toluidine blue, and dilute acids. Rogers found in scrapings from the walls of amœbic liver abscesses

that a solution of quinine, 1 to 1,000, failed to kill the parasite even after several hours. On the other hand, 1 to 500 solution stopped all movement of the amœbæ in from five to fifteen minutes. In order to test if such a strength would be effective when applied to the living wall of an abscess, a piece of such tissue which was full of active amœbæ was placed in a solution of 1 to 500 sulphate of quinine in normal salt solution, and scrapings examined every five minutes. In none of them were any living parasites found. In very *thick* walled abscesses, 1 to 100 solution of quinine was more satisfactory than 1 to 500.

Tuttle found that 1 to 10,000 bichloride of mercury and 1 to 100 nitrate of silver solutions check the motility but do not destroy the parasite except after prolonged contact. Saline solutions and 5 per cent. of the 15-volume peroxide of hydrogen in water also did not seem to destroy the amœbæ at body temperature. However, in the hands of this observer all of these substances when used at a temperature below 70° F. proved fatal to the motility and life of the parasite.

Musgrave and Clegg found that when a slant culture of amœbæ with bacteria was treated with a 1 to 2,500 solution of quinine hydrochlorate, the parasites quickly encysted and in from five to eight minutes many had broken up and disappeared. Ten minutes later cultures were made but no development of amœbæ occurred in the fresh inoculations, although the bacteria grew out well. In another experiment, performed in the same manner but with another amœba, a slight growth was observed. Acetozone, 1 per cent. acid to phenolphthalein, in solutions of 1 to 5,000 and 1 to 2,000, always killed the amœba in cultures. Thomas found that in cultures of amœbæ in symbiosis with cholera spirilla, boric acid, eucalyptol, ichthyol, oil of cassia, and infusion of quassia, had slight if any effect on the amœbæ. Tannic acid, 1 to 100, sulphate of copper, 1 to 2,000, permanganate of potassium, 1 to 4,000, and sulphate of quinine, 1 to 1,000, had a distinct moderate effect on the growth of the parasite and spirilla within thirty minutes. Alphozone, 1 to 1,000, permanganate of potassium, 1 to 2,000, sulphate of quinine, 1 to 500, nitrate of silver, 1 to 2,000, argyrol, 1 to 500, and protargol, 1 to 500, exercised a very marked effect on the growth of the cultures within thirty minutes, and, with the silver salts and alphozone, the action was plainly due to the destruction or inhibition of the growth of the symbiotic cholera spirillum. Thymol, 1 to 2,500, applied for fifteen minutes had the most marked effect, in some instances destroying the amœbæ, while exercising only a moderate effect on the cholera spirilla.

In regard to special *physiological processes* of dysenteric amœbæ, little is known. We are aware that certain definite secretions occur in the protoplasmic body, some of which evidently go to make up the mantle which forms about the parasite in encystation. It has been supposed by some that the engulfing of certain substances in the protoplasm—red blood corpuscles, bacteria, granular material, etc.,—occurred for the purpose of nourishment. Some have thought that the pigment masses which amœbæ sometimes contain are the remnants of partially digested red cells. This may be true, but no proteolytic enzymes have as yet been isolated, though Mouton has obtained a proteolytic ferment, resembling trypsin, from cultures of an amœba isolated from garden earth, and grown in symbiosis with *Bacillus coli communis*.

Distribution of Amœbæ in the Body.—Besides the intestine and neighboring tissues, the abdominal cavity, abscess of the liver, lung, and pleura, amœbæ have been found in the following pathological conditions: in ascitic fluid in cases of abdominal tumor; in necrosis of the jaw-bone; in abscess of the mouth; and in disturbances of the bladder and urine. Celli and Fiocca reported their cultivation from the larynx and lungs in cases of tuberculosis, and Gross and Sternberg found them in tartar scraped from the teeth. Frequently when present in the bladder a sinus leading into the rectum (as has been true in several of our cases) is found, or one has previously existed, but this is not always the case.

Classification.—Some observers have believed that more than one species of amœbæ occur at times in the intestine of man, and some have considered that not all are pathogenic but that some are harmless saprophytes. Kartulis, in reply to Grassi's communication, in which it was stated that amœbæ had been found in the stools of healthy persons, asserted that these organisms were not of the same variety as those which he had found in dysenteric cases in Egypt. However, he did not definitely prove this assertion. Councilman and Lafleur, believing on account of the number of observers who had found amœbæ in the stools of healthy persons that there might be more than one species encountered in the human intestine, proposed the name *amaba dysenteria* for the pathogenic variety, and reserved the one of *amaba coli* for the non-pathogenic organism of the normal intestine.

Quincke and Roos, in 1893, believed that they could distinguish three varieties of amœba. (1) *Amœba coli* Lösch, or *amœba coli felis*, which measured from 20 to 25 μ in diameter, possessed a finely granular plasma and a spherical nucleus, and contained blood corpuscles in the endosarc. Its cysts were spherical and presented a double contour. It was found in the stools of human amœbic enteritis, and upon injection into cats was pathogenic for these animals. (2) *Amœba coli mitis* was somewhat larger than (1), (40 μ); its protoplasm was coarsely granular and contained vacuoles. The nucleus did not have such a sharp contour and its motility was less. Included red blood corpuscles were never seen. This variety was also obtained from the stools in human intestinal disturbance but was found to be non-pathogenic for cats. (3) *Amœba intestini vulgaris* was found in the stools of a healthy man. It was morphologically similar to the second and not pathogenic for cats; but since it was found in a healthy individual, the authors considered it a third species.

Kruse and Pasquale, after numerous inoculation experiments performed on animals, distinguished two varieties of amœbæ found in the human intestine. They adopted the name of *amœba dysenteria* (Councilman and Lafleur) for the pathogenic variety, and *amœba coli* for the harmless one occurring in the stools of healthy persons. The latter they observed in their own stools when no symptoms of disease were present.

Celli and Fiocca have described six different varieties of amœbæ found in the human stools. (1) *Amœba lobosa* var. *guttula* measured from 2 to 4 μ in diameter, the smallest forms from 1 to 2 μ . It possessed a hyaline ectoplasm and blunt motile pseudopodia. (2) *Amœba lobosa* var. *oblonga* was double the size of the former variety and contained one or two non-contracting vacuoles. Its pseudopodia were short and

compact and oblong in shape. (3) *Amœba spinosa* (n. sp.). This variety was found in the healthy and dysenteric stools of man and also in the intestine of guinea-pigs and frogs. It had little motility. It measured from 6 to 10μ in size. There was little ectoplasm and the entoplasm contained from 1 to 7 non-contracting vacuoles. Cystic forms were observed. (4) *Amœba diaphana* (n. sp.) was also found in the dysenteric intestine. The ecto- and entoplasm was very difficult to distinguish. It showed very active motility and measured from 0.5 to 2μ in diameter. (5) *Amœba vermicularis* (Weisse) was found in the dysenteric intestine, and also in the vagina of healthy women and of those suffering from carcinoma. It varied from 4 to 6μ in length and was 1μ in breadth. No differentiation between ecto- and entoplasm could be made out and it contained no vacuoles. (6) *Amœba reticularis* (n. sp.). The form of this species was very constantly oval; the pseudopodia were angular and their movements slow; the organism measured from 2 to 4μ in diameter. There was no visible nucleus. The protoplasm was hyaline and homogeneous. Celli and Fiocca regarded none of these species as the cause of dysentery.

In the earlier work in Manila it was thought that at least two varieties of amœbæ found in the human stools could be distinguished—amœba dysentericæ and amœba coli. This differentiation was based primarily upon the pathogenic action, as with one species found in the stools of dysenteric patients typical lesions could be produced in cats, and with another, from the fæces of persons with apparently no intestinal disturbance, we did not succeed in obtaining any lesions. With still a third amœba which developed in cultures of straw infusions, no pathological changes were produced upon injection into animals. Having observed these differences, other points of differentiation were sought for. The most striking of these was that in the dysenteric amœba the distinction between endosarc and ectosarc could be readily made out, and that in the harmless one, the protoplasm of the ectosarc was not nearly so refractive. The nucleus of the former was eccentrically placed and could best be made out in stained preparations, while in the latter it was small and compact. The only other differences noted were that the amœbæ found in the stools of apparently healthy individuals were never seen to contain red blood corpuscles, and they also seemed generally somewhat smaller than the dysenteric amœba, since in a large number of measurements their diameter was usually less than 25μ , and in the dysenteric stools the amœba sometimes measured as high as from 35 to 50μ in diameter. Shiga later described amœba dysentericæ as from three to five times as large as amœba coli. However, the size of the parasites cannot longer be regarded as an *aid* in the separation of the species, since a number of competent observers have reported very small amœbæ as the only parasites present in undoubted amœbic dysentery. Moreover, the size of the organism may greatly change in cultivation and very small amœbæ may become large. Further observations suggest that animal experiments are often misleading, as one frequently encounters failures when undoubtedly employing the dysenteric species; and unless large series of inoculations are performed with each organism, the results are likely to be doubtful or misleading. Since pure cultures of amœbæ cannot be obtained except in the contents of sterile liver abscesses in which

other toxic material is probably present, many observers decline to accept the pathogenesis of an amœba as a point in differentiation. However, Schaudinn¹ has described additional details, particularly in encystation and reproduction, by which these organisms may be definitely separated.

Schaudinn believed that under the name of amœba coli, various authors have referred to two entirely distinct organisms which differ so much in their manner of development and reproduction that they could even be placed in different genera. One of these forms lives commonly in the intestine of healthy man but can also exist in the dysenteric intestine with the second species. The latter he found only in cases of dysentery of tropical origin and with it he produced ulceration in the large intestine of cats by feeding the encysted forms. He points out that the harmless amœba is the one which has been carefully studied and described by Casagrandi and Barbagallo, who also demonstrated its non-pathogenicity. From the description given by these authors, Schaudinn was able to recognize that he was encountering the same amœba, and he has been able to confirm their work entirely. Yet he was unable to say, from the published descriptions, whether the species which Löscher and other observers have described under the name amœba coli was the same as that which Casagrandi and Barbagallo had studied. These latter authors named the form they encountered *entamoeba hominis*, believing that it was the same form which Löscher had described. Schaudinn pointed out that since it was necessary to establish a new genus and their description was the first accurate one of the organism, the name of "*entamoeba*" should stand, but as they supposed they had the same form as Löscher the name "*coli*" should be substituted for "*hominis*." Schaudinn infected himself on two occasions by ingesting the cysts of this harmless amœba. In both cases the artificial infection was controlled by the examination of his stools for two months. Young cats were also infected for the purpose of the study of cyst formation.

With reference to the structure of this harmless amœba (*entamoeba coli*), he emphasizes that during rest the characteristic differentiation between ectoplasm and entoplasm does not exist and that it is only in the formation of pseudopodia that the hyaline appearance of the former is noted. The nucleus is vesicular, spherical, and provided with a thick, dense, nuclear membrane. The nucleolus consisting of plastin and chromatin occupies its centre, while the remaining granular chromatin is distributed in the achromatin network. The multiplication takes place either by simple division or through spore formation (schizogony). In the former case the nucleus become contracted in the centre, assuming a dumb-bell shape, and parts amitotically. Then the entire cell divides after the separation of the daughter nuclei. In reproduction by schizogony the chromatic substance of the nucleus separates into eight parts, which after dissolution of the nuclear membrane become distributed in the protoplasm as daughter nuclei. The soft protoplasm then divides into eight young amœbæ.

Schaudinn recommended the half fluid stools as most favorable for the study of the encystation of this organism. He stated that there are few objects so favorable for nuclear study in the living cell as these cysts,

¹ *Arbeiten aus dem Kaiserlichen Gesundheitsamte*, Bd. 19, 1903.

whose plasma is entirely clear of all foreign bodies, and, with proper artificial light, the nucleus appears as sharp and plain as in a stained preparation. Already in the resting state, if they do not contain many foreign bodies, the nucleus can always be clearly recognized. In encystation the foreign bodies are cast out of the plasma, which becomes entirely clear and transparent, and the nucleus then can be even more clearly seen.

Entamæba histolytica (n. sp.); this was found by Schaudinn in the stools of those suffering with dysentery contracted in the tropics. It is different from the harmless form; the plainly developed ectoplasm is more strongly refractive and hyaline than in *entamæba coli*. In the latter form the hyaline pseudopodial plasma in contrast to the remaining plasma is not well differentiated and is much less refractive than in *entamæba histolytica*, in which there is always a plainly developed ectoplasm existing as a plasma zone and possessing a stronger refraction than the entoplasm. Jürgens had already called attention to the glassy hyaline appearance of the ectoplasm in the dysenteric amœba, and this property, Schaudinn stated, is most important in the living amœba and to it may be attributed special phenomena. The harmless *entamæba coli* with their soft pseudopodia cannot enter into the healthy mucosa of the intestine but the dysenteric amœba is able, by means of its stiff hyaline ectoplasm, to penetrate between the epithelial cells and to separate them from one another. Schaudinn, in freshly cut sections of the intestine of infected cats, watched for an hour the process by which this protozoön separates the epithelial cells from one another.

The nucleus of *entamæba histolytica* is very difficult to recognize in fresh specimens. Its shape changes very easily and it often becomes stretched out. Its position is always eccentric. The parasite multiplies by division and budding. Under unfavorable conditions for the organism, spores are formed. The usual method of reproduction is as follows: The nucleus expels some chromatin into the protoplasm and finally itself degenerates. In the encystation in vivo it is, under the eye of the observer, later expelled and cut off. Small spherical bodies possessing a diameter of from 3 to 7 μ , and presumably containing some of the particles of chromatin, become formed in the cyst. The plasma then appears at the periphery protruded and bulged out and these buds are cut off finally in the form of balls which show a concentrically arranged filamentous structure. They soon secrete an opaque membrane and all further process of development becomes invisible. The rest of the amœba dies. The small round forms Schaudinn believed bring forth in the course of time a new infection, and this he showed by his experiments on animals. While he observed spore formation he never saw the eight nuclear cysts in the development of *entamæba histolytica*. On one occasion when he did find these cysts in an infection with *entamæba histolytica* he was able to prove later that a double infection with both amœbæ existed.

Craig points out that since Councilman and Lafleur accurately described the amœba dysenteriae, the name "*histolytica*" should be dropped and this species should be known as *entamæba dysenteriae*. However, Schaudinn was the first to call attention to the essential differences by which these two organisms might be separated from a zoölogical stand-

point, for Lafleur in his later paper stated that no definite morphological differences had been found between the amœba occurring in the stools of healthy persons and in patients suffering with dysentery.

Lesage gives the same characteristic distinctions for entamœba histolytica that Schaudinn had mentioned. Upon staining these amœbæ in cultures by Laveran's method, the protoplasm colored itself lightly and uniformly except at one point near the periphery where it (the nucleus) stained more deeply. In the cysts the surrounding membrane did not stain and there was a clear space between it and the protoplasm. The latter during development was sometimes seen to be almost separated into three portions, each of which enclosed a lightly stained nucleus.

Craig in his most recent work also confirms Schaudinn's observations. He says in addition that the amœba dysenteriae is larger, and that when stained a diagnosis can be made by observing that the ectoplasm colors much more intensely than the entoplasm, while in entamœba coli the opposite is true. The latter form is not actively motile in the stools and a vacuole is seldom seen.

Occurrence of Amœbæ in Healthy Persons.—The presence of amœbæ in the stools of apparently healthy individuals has inclined many authors to believe that all amœbæ are without etiological or pathological significance. Among the more striking of these observations in recent times may be mentioned: Schuberg, in 1893, found amœbæ in the stools of 10 out of 20 healthy persons to whom a dose of Carlsbad salts had been given. Kruse and Pasquale, in 1894, when perfectly healthy, observed amœbæ in their own fæces and in those of 38 persons either healthy or suffering with diseases other than dysentery. Upon some of these, fresh autopsies were performed and the intestine carefully examined. In 1899, the writer examined with Musgrave in the Philippine Islands, persons who had no dysentery nor any history of the disease and found amœbæ in the fæces in 4 per cent. A dose of Rochelle salts had been given by the mouth previously. Schaudinn recently found amœbæ which he considered harmless in the stools of 34 of 68 healthy people in East Prussia, in one-fifth of the cases examined in Berlin, and in 256 out of 385 in Austria. Schaudinn twice infected himself with this amœba and controlled his fæces before the infection for two months in order to be sure that his stools were free from these parasites. After infection he suffered from no intestinal disturbance. Craig in 1905, examined 200 patients not suffering with dysentery and found amœbæ in 65. However, in other regions observers who have sought at random in the stools of healthy individuals for these parasites have failed to find them. Notable among these investigations may be mentioned those of Dock in the United States and of Zorn in Munich.

There are periods in the course of amœbic dysentery, particularly in the earlier stages, in which symptoms are entirely lacking. Hence when amœbæ are found in the stools of healthy individuals we cannot say that they are not suffering with an early or latent form of the disease, or that the malady does not exist in its incubation period, unless we follow them over long periods of time in which no disease develops. The writer had opportunity, among private patients, to study some instances. One occurred in a chemist of our laboratory who in August asked that an examination be made of his fæces, as he had a slight attack of diarrhœa

the day before. An unusually rich infection with amœbæ was found and he promised to undergo the usual local treatment but next day as he felt perfectly well, the diarrhœa having entirely ceased, he remonstrated against beginning it. However, he did take enemata for about a week, but subsequently did not pursue any further treatment. His stools were many times examined and always infection with amœbæ was demonstrated, the last being on December 10th. Two examinations made towards the end of January showed that the amœbæ had disappeared. During the period from August to December he was without a single manifestation of disease. The stools were formed and apparently normal. He has been perfectly well since.

It would appear that there are some individuals, apparently perfectly healthy, who harbor amœbæ in large numbers for long periods without any unfavorable symptoms. It is not necessary to suppose that lesions are always present, although in some, lesions may exist which we cannot always be aware of during life; and the questions arise, are these instances of natural resistance or immunity against the parasite, or are they instances in which the parasites are unable to exert any harmful action until the proper symbiotic bacteria appear in the intestine and are only awaiting this moment to become pathogenic, or are they cases in which the organisms are still incapable of producing any injury until through some mechanical disturbance a small erosion in the mucosa occurs, or are they instances of infection with an amœba harmless to man? With our present knowledge some of these questions are very difficult to answer. Some incline to the belief that all amœbæ are pathogenic and maintain that in every case in which infection is found, even though there be no symptoms, local treatment should be instituted and pursued until the amœbæ disappear. Musgrave quotes his recent experiences in support of this. He found in the examination of the stools of 300 prisoners in Manila that 101 were infected with amœbæ; 61 of these in whom the parasites were found were suffering with dysentery, but the other 40 stated they had no diarrhœa. During the next two months 8 of the 40 cases died of intercurrent disease, and satisfactory evidence of amœbic infection was present in all. Three and a half months later all of the remaining 32 cases (with the exception of 2 discharged from the prison) had amœbæ in their stools and were suffering with dysentery. However, this does not disprove the existence of a harmless amœba or the presence of such an organism in the intestines of his patients in connection with the dysenteric amœba. Since Schaudinn has shown us that zoologically two distinct species of amœba exist in human stools, it is necessary that careful studies be made of each of these species, that the cases in which they are present singly and conjointly be separated and carefully observed. Natural immunity should be considered in this study. The writer has undertaken this differentiation in cases of amœbic infection, but is not prepared at this time to speak with certainty as to the entire non-pathogenesis of the so-called *entamoeba coli*. Theoretically it would seem not unlikely that should erosions in the mucosa occur, the amœbæ might, by their mechanical movements and wanderings and by carrying adherent intestinal bacteria with them into the broken epithelial layers, aid in continuing the existing lesions. There are, theoretically, from the description which Schaudinn has given, obvious

reasons for supposing that *Entamoeba histolytica* is the more harmful organism for man; but it seems that any classification into pathogenic and non-pathogenic amœbæ based alone upon the differences in the movements and character of the ectoplasm should be accepted with caution. Before coming to any more definite conclusion about the relative pathogenicity of *Entamoeba histolytica* and *Entamoeba coli*, a more careful investigation should be made of the secretory products of these parasites and a search made for their enzymes, soluble and endotoxins, etc. We know nothing yet of the relative virulence of amœbæ or whether their pathogenesis under certain conditions may be increased by long periods of existence in the human intestine.

Occurrence of Amœbæ in the Stools of Those Suffering with Other Diseases than Dysentery.—Another argument advanced against the etiological significance of amœbæ in dysentery, and brought forward as recently as 1902 by Duncan, is the fact that these organisms have been found in the intestines of those suffering with other diseases, such as chronic diarrhœa, cholera, intestinal tuberculosis, typhoid fever, hæmorrhoids, etc. In many of the reported cases the hæmorrhoids might probably be regarded as a complication, and the chronic diarrhœa as stages of pathogenic amœbic infection. But it should also be borne in mind that in some of these the *Entamoeba coli* may have been the form of protozoön present. Lafleur mentions a case of malignant disease of the stomach in which the light fluid movements contained many active amœbæ but no ulceration of the bowel existed, and Kruse and Pasquale found no lesion at autopsy in some of their patients in whom amœbæ were present.

In the tropics, where amœbic dysentery is so common and frequently a chronic disease of long standing, concomitant occurrence with typhoid fever, cholera, or tuberculosis, is not so very uncommon. In the writer's series of 100 fatal cases of amœbic dysentery in soldiers there were 4 cases of concomitant infection with typhoid fever, in 1 of which death occurred from a perforation in the ileum. The third case of cholera, at the beginning of the great Manila epidemic in 1902, was one of double infection with amœbic dysentery and this disease, and during the outbreak a number of others were found.

The Non-occurrence of Amœbæ in the Stools of Dysenteric Patients.—Many observers have advanced the argument that since amœbæ are not found in the fæces or in the intestines of those suffering with tropical epidemic, or sporadic dysentery, these organisms are not the cause of the disease. Shiga in Japan, Flexner and the writer in the Philippines, and Leonard Rogers in India, have shown that tropical dysentery consists of at least two forms, one due to a species of amœba and the other to a species of bacterium. These conclusions have been confirmed also for temperate climates by a number of observers in the United States and in Europe. In addition to these forms there is a third catarrhal dysentery, which is seen occasionally in the tropics and has a varied etiology. It is occasionally indistinguishable clinically from amœbic dysentery.

Inoculation Experiments.—Several methods have been chiefly employed. (1) The direct injection into the rectum of fæces containing the parasites. In this manner positive results have been obtained in cats and dogs. It is to be noted that in these experiments not all the

inoculated animals became infected, and that single experiments and those in which unsuitable material is employed are likely to fail. However, there is no doubt that lesions may be produced in the large intestine in cats by this method, though there are often many difficulties. (2) By feeding encysted forms of amœbæ. Casagrandi and Barbagallo, Calandruccio, and Schaudinn, fed themselves encysted amœbæ, produced infection and reobtained the amœbæ from their stools. They had no symptoms of disease following the infection. They also infected cats by feeding encysted cultures of this parasite but obtained no symptoms of disease. Upon feeding the cysts of *Entamoeba histolytica* to cats, Schaudinn obtained dysentery and ulceration of the large intestine in which were found numerous amœbæ. Quincke and Roos fed stools containing encysted amœbæ to two cats and obtained infection and amœbic ulceration, which they observed at autopsy. Musgrave fed encysted amœbæ in cultures with bacteria to monkeys and obtained, in a small percentage of the cases, dysentery and ulcerations in which amœbæ were found. The bacteria which were fed with the amœbæ were not recovered from the stools, showing that it was not these microorganisms that had produced the disease.

Against these experiments, in which bacteria together with the amœbæ were employed, being used as an argument in favor of the pathogenesis of the parasites, objection was naturally urged. Therefore attempts were made to employ material in which amœbæ were present without microorganisms. Kartulis, and Kruse and Pasquale, used the contents of sterile liver abscesses and produced dysentery and ulcerations in the intestines of cats by rectal injections. They, however, stated that while the lesions in their most successful experiments bore in many points a striking resemblance to those seen in man, they were not identical. In 1899, the writer obtained dysentery and perfectly typical amœbic ulcerations in the large intestine of cats by the injection into the rectum of portions of the contents of a liver abscess which contained living amœbæ but was otherwise sterile. These lesions were perfectly typical of the lesions seen in man. Many of the ulcers showed a distinct undermining of the mucosa and a round-cell infiltration of the submucosa with numerous amœbæ at the base of the ulcers. Some of these specimens are now in the Army Medical Museum in Washington. These experiments are suggestive of the pathogenesis of this species of amœba.

It is possible that toxic substances may be introduced with the amœbæ in the pus of these liver abscesses, and it might be argued that these cause erosions of the mucosa. However, a chemical substance alone could hardly produce the typical anatomical lesions of the disease which are so peculiar to amœbic infection alone and which no one has produced without amœbæ. Probably as much as could be expected has been gained from experiments on animals. Before leaving the subject it is interesting to note that both the lower monkeys and orang-outangs contract the disease naturally. At one time as many as four or five of our laboratory animals have suffered with naturally acquired infection. One of our imported orang-outangs recently died of a natural infection of the disease.

Source of Amœbæ and Mode of Infection.—In Manila the greatest source of infection is the water-supply. Amœbæ were frequently culti-

vated from it in large numbers in 1902, but no attempt was made to demonstrate their pathogenicity. In 1904, Musgrave injected directly into the exposed cæcum of a monkey, by a hypodermic syringe, an old culture of an amœba growing with bacteria that had been isolated from the city water-supply. A month later violent diarrhœa developed, and amœbæ, some of which enclosed red blood cells, were present in the stools. The animal was killed and small ulcerations were found in the large intestine. However, it must be stated that with cultures of this same amœba he was unable in a few experiments to infect cats by rectal injection. From a practical standpoint it is demonstrated daily that it is very easy to live in Manila and avoid infection with amœbæ, provided one avoids infected drinking water. Those who never drink local water but use only the better imported bottled aerated waters are not attacked with amœbic dysentery. Open reservoirs and tanks containing drinking water may be polluted by the excreta of infected monkeys. Lettuce leaves contaminated with amœbæ may be one source of infection.

It is very probable that not all of the amœbæ found in our water-supply are pathogenic, and it is also probable that those who ingest the pathogenic form do not all suffer with the disease amœbic dysentery. Dilute acids quickly kill the amœba, and it is probable that many of those ingested are destroyed in the stomach. Natural and, in the natives, acquired immunity from constant exposure to the disease may also exist, and probably in these cases the disease results only when the system is overwhelmed with very large numbers of the parasites or when it is weakened by other disease.

Other Organisms Encountered in Amœbic Dysentery.—Other protozoal organisms common in the intestine in amœbic dysentery are the trichomonas, *Cercomonas intestinalis*, and *Megastoma entericum*. These, when present in this disease in very large numbers, probably by their rapid mechanical movements, act as an irritant to the already inflamed mucosa. Other animal parasites which are found not infrequently in the intestine of those who suffer with amœbic dysentery in the tropics are the *Tænia saginata*, *Ascaris lumbricoides*, the *Tricocephalus trichuris*, *Uncinaria duodenale*, *Strongyloides intestinalis*, and *Oxyuris vermicularis*. In Egypt the ova of *Bilharzia hæmatobia* may be also present in the stools. When these parasites are present the cases may be regarded as a multiple infection. Schaudinn has stated that certain species of bacteria found in dysentery apparently exert a distinctly harmful influence upon entamœba coli and monads which may be present in the intestine at the same time. This, however, is not true of *Bacillus dysenteriæ* and the dysenteric amœba, since in some cases we find both of these parasites producing lesions side by side in the large intestine.

Bacteriology.—Krusse and Pasquale investigated the organisms found in 14 cases of the disease and isolated streptococci, *Staphylococcus pyogenes*, typhoid-like bacilli, *Bacillus pyocyaneus*, and *Bacillus clavatus*. None of these was present so constantly or in such numbers as to suggest a specific relation to the disease. Of 6 cases in which pure cultures of *Bacillus pyocyaneus*, *Bacillus clavatus*, the streptococcus, or typhoid-like bacilli, were introduced into the rectum of cats, in 5 the results were negative; in the sixth, where the streptococcus was employed, there was

no dysentery, but a catarrh of the whole intestinal tract and a general septicæmia.

In 26 fatal cases in plate cultures from the large intestine several varieties of the colon bacillus were the only organisms found constantly present. We were unable to produce dysentery or any lesions in cats by rectal injection of cultures of the varieties of the colon bacillus encountered. In 76 fatal cases cultures were made from the solid organs. The bacteria encountered were streptococci and staphylococci, *Diplococcus pneumoniae*, colon bacilli, the typhoid bacillus, and *Bacillus ærogenes capsulatus*. The most striking fact demonstrated by these examinations was that 5 per cent. of the cases succumbed from a general terminal infection with the *Staphylococcus* and *Streptococcus pyogenes*.

Pathology.—The Large Intestine.—The large intestine is chiefly involved. The most striking feature in chronic cases is the great thickening of its walls. This may be confined to the submucosa or involve all the coats. It is always more marked in the submucosa and is due to a general œdema and localized areas of thickening. The other characteristic lesions consist chiefly of hemorrhagic catarrh, of raised hemispherical areas of infiltration protruding above the level of the surrounding mucosa, and of at least three forms of ulceration. Frequently a diphtheritic process is added to the amœbic one. The lesions may affect the whole large intestine or a portion only, as the cæcum, the hepatic or sigmoid flexure or the rectum. Generally in fatal cases the large bowel is affected throughout. In some the intestine is riddled with ulcers; in others a moderate number is scattered through it. There appears to be no particular portion of the large intestine that is definitely predisposed to the infection.

We may consider the lesions from the beginning of the pathological process. The amœbæ insert themselves either between the cells of the normal mucosa, along the interglandular substance, or into small erosions which may exist in the intestine from other causes. They next generally work their way through the muscularis mucosæ by the lymph channels and finally enter the submucosa. Here migration and reproduction take place and infiltration with round cells and œdema results. The mucosa becomes bulged out and small pin-head-sized dots appear on the interior of the bowel. Should a small capillary hemorrhage result in these areas, as frequently happens, the nourishment of the overlying epithelial cells becomes disturbed, and these, perhaps partly by digestion, become gradually disintegrated, softened, and cast off. The œdematous submucosa is then exposed, which may appear yellowish from infiltration with round cells or yellowish red if the blood cells still remain in this area. Thus the earliest erosion is formed and becoming exposed to the fæcal material and bacteria in the intestine, an increased number of cells accumulate, and if pus cocci are present more or less true suppuration occurs.

The process is limited in extent by the surrounding tissue, which is well supplied with blood and hence red margins to the erosions or ulcerations exist. The amœbæ on the surface die or are cast off into the lumen of the intestine but others migrate deeper and laterally into the submucosa. Should no hemorrhage occur early beneath the small bulgings of the mucosa, the areas increase in size through the œdema and round-celled infiltration; hence the diameter of these erosions and small

ulcerations when first seen depends upon how long the overlying mucosa remains intact before becoming necrotic, disintegrated, and cast off. They therefore generally vary in size from 2 or 3 mm. to about 2 cm. In some cases the nodular projections are intact and raised above the surface of the mucosa, and on incising them they may be observed to contain a pale-yellow or grayish-yellow viscid material. The earliest lesions are obviously rarely seen at human autopsies, but may be studied in infected cats which have been killed a day or two after inoculation. In many of the ulcerations that have originated from nodules which reached 1 or 2 cm. or more in size before opening, we may see evidences of the primary nodular formation from the fact that the margins are raised and thickened and in many cases undermined. Moreover some of the ulcers have a distinct crater-like appearance, with a small opening in the centre, which may be pin-head in size or so large as to freely expose the cavity. About the edges of many of these ulcers there exists a dark-purplish or reddish ring of congestion. The mucosa between the ulcers in early cases may appear perfectly normal, but in later ones a desquamative or hemorrhagic catarrh may be present. Whether this is due to certain soluble products of the amœbæ acting upon the surface of the mucosa, or to their mechanical movements upon it, or to some other process, we do not know. The ulcerations increase in size, probably owing to the combined action of both amœbæ and bacteria. The floors and edges become softened, necrotic, and covered with a mucous exudate. In the earlier stages the ulcers are round or oval and placed with their long diameters transversely to the lumen of the intestine. Later they may become irregular in outline. The diameter of the large ones probably depends chiefly upon how laterally the amœbæ have spread out in the submucosa, and their depth mainly upon the depth the amœbæ have penetrated into it before the overlying mucosa was cast off. In the former case the shallow ulcerations of several centimeters in diameter with irregular margins are formed, whose edges are usually reddened and surrounded by apparently healthy mucosa and whose floors are usually necrotic and covered with a yellowish or greenish more or less mucopurulent exudate. From either of these two types of ulcer the more serious lesions usually develop, so that extensive surface ulcerations whose floors are formed usually of submucosa result, or deeper ones with smaller diameters whose bases consist of submucosa, muscular coat, or even peritoneum. It is in the ulcerations of moderate depth, owing to the burrowing of the amœbæ in the submucosa beneath the mucosa, that the characteristic undermining of the borders of the ulcers results. This becomes particularly marked owing to the fact that the muscularis mucosæ is not infiltrated and destroyed to the same extent as the submucosa and hence holds up the mucous membrane. In the more extensive ulcerations, necrosis and undermining of the muscular tissue also take place, whereby frequent sinuses are formed beneath the mucous membrane, and portions are dissected out and cast off into the lumen of the intestine as sloughs.

A third form of ulceration sometimes seen is that in which the lesion extends only partially through the mucosa and results from a gradual disintegration of the epithelial cells and not by necrosis and sloughing of the underlying tissues. The bloodvessels of the mucosa are likely

PLATE V



Colon in Amœbic Dysentery.

PLATE VI



Colon in Amoebic Dysentery.

here to be more dilated and filled with blood. These ulcers may develop both laterally in the mucosa and in depth into the submucosa; but there is not in either case the characteristic undermining that is observed in ulcerations of the other type, though the round-celled infiltration in the vicinity is frequently even more extensive. When these surface ulcers extend only into the mucous membrane, amœbæ are rarely found in them, but are sometimes encountered at their margins lying in or between the glands. It seems probable that this form of necrosis and ulceration is a direct extension into the mucosa of the process which begins as a hemorrhagic catarrh. It may be due to the action of soluble toxic products of the amœbæ aided later by the intestinal bacteria. A somewhat similar process is observed in the liver, which consists of an extensive necrosis of areas of liver tissue which contain no amœbæ and which are situated in the vicinity of the abscess. Complete breaking down and softening seems to occur only when the amœbæ actually come in contact with the cells, and this may be due to the action of an intracellular toxin.

The amœbæ wandering in the submucosa and carrying with them adherent bacteria cause continuous disturbance. The parasites themselves seem to be responsible chiefly for the cedema and round-celled infiltration, and softening and breaking down of the tissues. The bacteria cause additional leukocytic infiltration and necrosis. The action of the latter is manifested chiefly in the more superficial ulcerations where the amœbæ may be scanty upon the surface. The parasites in addition cause early infiltration with round cells of the walls of the capillaries and veins, which condition is followed by softening and complete disorganization of these structures. It is in this way that much blood appears in the stools. The amœbæ may even penetrate the walls of the veins, and are frequently found inside these vessels, some of which they may have entered directly or been carried from the capillaries through the lumen of the vessel. In this way the veins may become thrombosed. The arteries in the neighborhood of the ulcer also frequently show thrombi, and in the chronic process evidences of endarteritis are found. The slow inflammatory process in the submucosa consisting of cedema, infiltration, and finally of proliferation of the fixed connective tissue cells, leads to great thickening in the bowel wall and hypertrophy of the vessels.

In certain cases the tissues seem little able to resist the infection, and large gangrenous ulcers result whose walls are soft and whose bases are formed of blackish or greenish sloughing tissue in which numerous cocci, bacilli, and sometimes amœbæ, are found. These changes are certainly not produced entirely by amœbæ, but are probably due chiefly to the bacteria which are present. Another process which is sometimes seen in cases of this disease is the diphtheritic one. It is also certainly partially if not entirely caused by the action of bacteria. When *Bacillus dysenteriae* is present the origin of the pseudomembrane is easily explained. Obviously the ulcerations in different cases and even in the same case may vary greatly in appearance in the active stage, according to the extent and manner of progression of the lesions, but they can usually be classified under one of the types which have been described.

The process of healing may best be studied in patients who have been under treatment for some time with the intestinal disturbance and pro-

gressing favorably but death has resulted suddenly from some complication. The ulcers may then be found with bases which are distinctly depressed and have a grayish or grayish-yellow color. Their margins, however, are raised above the bases, and are clear cut but are not usually swollen above the surrounding mucosa. When well advanced toward healing they are no longer softened. The surfaces of the ulcers are bathed in a serous fluid or covered with mucus. Healing takes place by the formation of fibrous connective tissue in the floors and by a gradual covering over with epithelium. If the lesions have been extensive old pigmented scars result.

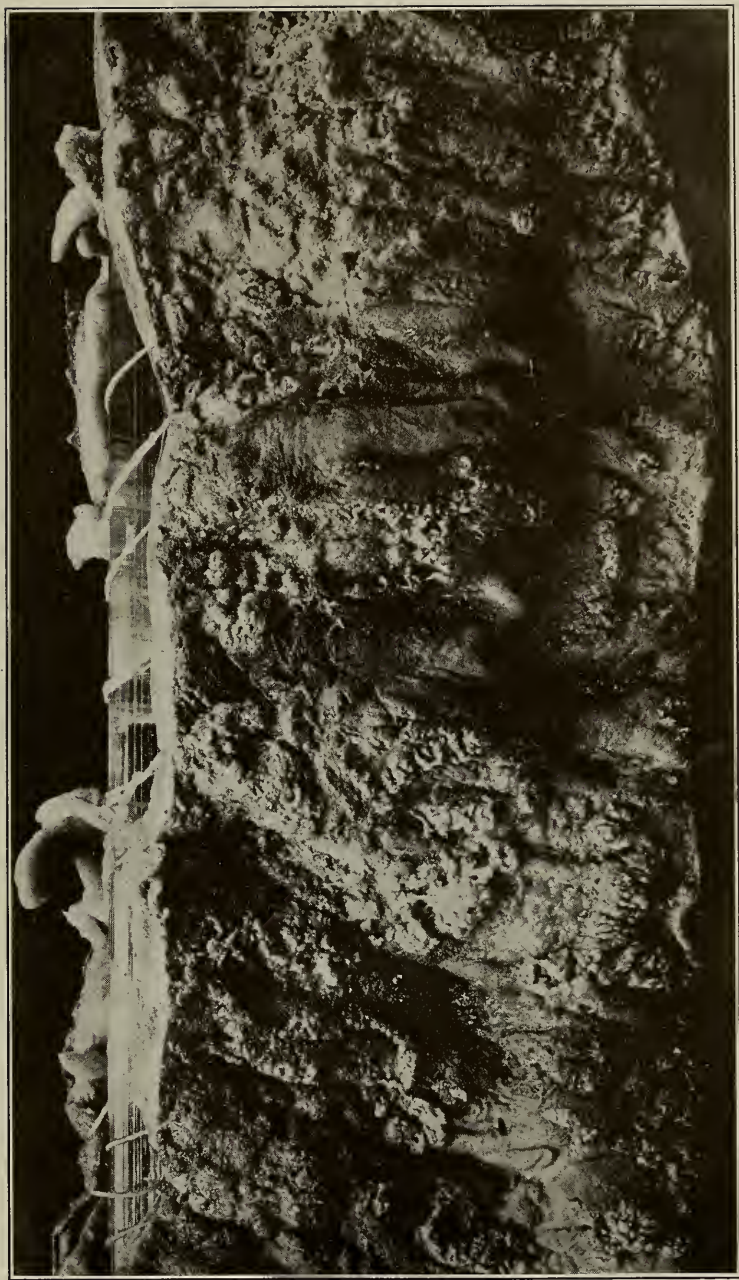
Peritonitis.—As has been pointed out, the amœbæ may wander freely through the submucosa and into the circular muscular coat, where they are frequently found along the intermuscular septa and between the muscle fibers, which they have evidently separated. The fibers themselves become swollen, granular, indistinct, and may appear without nuclei. They finally become infiltrated, break up, and disappear. The parasites also destroy the bloodvessels in this layer; the blood-supply is then cut off and more extensive sloughs are formed. They may next push along the intermuscular septa through the longitudinal muscle and produce the same changes. Should they approach the serosa similar changes to those seen in the submucosa take place in the subperitoneal coat.

In case many bacteria, particularly the pus cocci, now find their way into the tissue, deep sloughing gangrenous lesions are formed and perforation with general peritonitis frequently occurs. In other cases when few bacteria are present this may take place from violent peristalsis after adhesions are formed. However, in the latter instance, particularly when the floor of the ulcer is composed of muscular tissue and does not extend completely down to the serosa, the peritoneal coat, owing to the action of the amœbæ, becomes greatly thickened, not only from the œdema and infiltration but by the formation of considerable fibrin. This also occurs on the peritoneal surface, and so the intestine later becomes adherent to loops of the small bowel or to the omentum or abdominal wall and the adhesions so commonly found at autopsy in the chronic cases are formed. Occasionally general peritonitis will occur with no visible perforation, the amœbæ having penetrated the muscular coat and serosa and set up an inflammatory exudate which consists of an opaque gelatinous fibrinous fluid in which the amœbæ may be found.

It will be noted that one of the most striking points in the pathology of the infection is the absence of the usual products of purulent inflammation. Polymorphonuclear leukocytes are found in relatively small numbers in the tissues, and are never aggregated together in large groups unless many bacteria are present.

Microscopic study shows that the submucosa is very œdematous. Its interstices are widened and the lymph channels engorged. The fixed connective tissue cells are swollen, stain poorly, and often show fatty degeneration. In places where extensive necrosis has resulted the elastic tissue fibers remain last and stain well. In these areas much amorphous granular material is present and the cells lose their nuclei and stain poorly. In addition there may be a general liquefaction of the tissues. Extensive round-cell infiltration exists in the submucosa where but few

PLATE VII



Colon in Amoebic Dysentery.

polymorphonuclear leukocytes are usually seen. Plasma cells are present at times in considerable numbers, and eosinophiles are in some cases also fairly numerous. At the margins of the ulcers many of the epithelial cells show parenchymatous or mucoid degeneration. The mast cells are usually diminished in these areas. One may also observe that the ulcerations do not as a rule begin in the follicles, but these may become secondarily affected. The amœbæ are found in large numbers in the lymph spaces, in which case the endothelial cells in the neighborhood are proliferated and there is sometimes a fibrinous exudate inside the vessel. The parasites are also present in the ulcers, being most numerous in the submucosa along their bases and sides, in the zone of œdema and round-cell infiltration which borders the necrotic portion of the lesion. Bacteria are always most numerous in the upper necrotic layers of the ulcer, and when the pus cocci are present purulent inflammation frequently results. In these areas amœbæ are seldom found. Bacteria are also found, usually in small numbers, with the amœbæ in the deeper lesions.

Small Intestine.—Involvement of the lower end of the ileum sometimes follows from an extension of the process upward from the cæcum. The mucosa just above the valve is frequently hyperæmic and occasionally hemorrhagic. In only one of the writer's autopsy series did it show amœbic ulceration, though several other cases complicated with typhoid fever showed typhoid ulceration of the Peyers' patches.

Lymphatic Glands.—The mesocolic glands are frequently swollen, particularly where the lesions are extensive and extend deeply into the muscular coats. They may occasionally be hyperæmic or œdematous but are very rarely hemorrhagic, and in this respect offer a strong contrast to the condition of the lymphatics in bacillary dysentery. Microscopic examination shows that the lymph sinuses are more or less dilated, and there may be some proliferation of the connective tissue cells and a few plasma cells present. In rare cases necrosis may take place and bacteria may be present. The bloodvessels are usually normal. The small round cells are frequently increased in number.

The Kidneys.—The chronic cases sometimes show evidence of parenchymatous nephritis, which is rarely of extreme grade. The cells of the tubules are more or less granular and stain poorly, and albumin is sometimes found in the glomerular spaces. Occasionally the cells of the convoluted tubules and the glomerular epithelium are fatty, and in places desquamated. The *spleen* and the *heart* muscle are usually normal, and the *lungs* show no special changes peculiar to the disease except abscess of the right lower lobe, which, together with the lesions of the *liver*, will be discussed under the subject of hepatopulmonic abscess.

Musgrave has recently seen two cases of general infection with amœbæ.

Symptoms.—General Characteristics, Clinical Forms, Mode of Onset, Course, Duration and Termination.—The symptoms may vary so widely that in order to discuss the subject intelligently the cases may be grouped for convenience under the following divisions: (a) Mild cases and those of moderate intensity. (b) Cases with acute onset. (c) Advanced and chronic forms.

This division is purely an arbitrary one since no sharp lines of distinction can be drawn and the cases may pass from one to the other.

Moreover instances may occur which can be better considered partially under more than one of these divisions. While individual cases may vary widely there are some features which are very common in at least the majority. These are the irregular course, marked by periods of intermission and exacerbation, the appearance of mucus in the stools, and the tendency to chronicity. A phenomenon that is peculiar to the malady is the frequent occurrence of the amœbic liver abscess.

(a) *Mild Cases and Those of Moderate Intensity*.—Usually the patients are not able to tell exactly when they began to realize that they were not in good health. There may be complaint of some lassitude, of becoming easily tired, or of continuous slight headache; more or less indefinite abdominal discomfort and dyspepsia may be present. Slight intestinal disturbances consisting of moderate diarrhœa or of constipation may appear. Such symptoms may occur singly or in various combinations. These represent patients who, frequently in the tropics among the well-to-do people, consult the physicians for such minor ailments as have been mentioned and generally have no idea of the real trouble. Such vague symptoms may continue for months, and one may doubt whether they are all dependent upon the intestinal infection. Occasionally the abdominal pains become severer, or there may be an outbreak of diarrhœa which causes the physician to examine the stools, when amœbæ, sometimes mucus and even red blood cells, are found. A great many of these infections remain undiscovered for a long time. Such have been described under the name of latent or masked forms of the disease. Robust men may have the disease for a month or two without being aware that they are suffering from a serious malady. Indeed some may go to autopsy with advanced intestinal lesions in whom the symptoms have not been sufficiently prominent to attract attention. They may never advance beyond this latent stage; either under some simple treatment by the mouth, or even without treatment, the patient may overcome the infection and the parasites disappear from the stools. In by far the greater number, however, some of the symptoms sooner or later increase in severity, and in the event of recovery not taking place they may pass gradually into either those of moderate intensity or those with acute onset. The two symptoms most likely to attract attention are diarrhœa and abdominal pain. In those patients who are constipated the latter may be the first symptom; or indigestion and gradual loss of weight may be equally prominent. Palpation of the abdomen sometimes reveals tenderness, but this is by no means constant. As the lesions in the large bowel increase, the symptoms of intestinal disturbance usually become more marked, abdominal soreness appears, and the stools become more frequent and contain mucus and even blood. If they are properly treated the disease does not usually progress to the chronic stage, and this particularly is why the name "dysentery" is not an entirely apt one for the malady and why "amœbic colitis" would perhaps answer better. Musgrave has proposed the term Amœbiasis to cover all grades of the infection.

Even if treatment is not instituted a small proportion of this group may entirely recover, frequently after several recrudescences of more or less active diarrhœa; but the majority pass gradually to the chronic form, or occasionally acute symptoms develop. Sometimes the abdom-

inal manifestations may be so insignificant as entirely to escape notice, or the appearance of a liver abscess first attracts attention.

(b) *Cases with Acute Onset.*—Obviously it is not correct to consider all of these as acute cases. Some are really acute almost from the beginning, but others may have existed for some time as latent, mild, or moderately severe infections. The symptoms are frequently not in accord with the lesions; ulcerations may exist and become well marked before there is a sudden outbreak of the diarrhœa. Very abrupt onset may occur from the formation throughout the large intestine, but particularly in its lower portion, of very numerous small and superficial ulcerations, or from secondary infection with streptococci or *Bacillus dysenteriae*. Cases with diphtheritic or gangrenous lesions may be classified clinically under this division, and in the latter instance portions of sloughing tissue may be passed in the stools. At the onset there may be from 15 to 50 or more bloody mucous movements in twenty-four hours. Colicky pains in the abdomen with tenesmus develop; fever, nausea, and vomiting may appear; great exhaustion sets in; the heart action becomes feeble and either death results, or the condition temporarily improves and gradually assumes the chronic form. It is in this form that wild delirium may develop before death.

(c) *Advanced and Chronic Cases.*—In the advanced stages of the disease the symptoms become well developed. The movements become more frequent and usually contain much mucus and frequently blood. Their number may vary from 2 or 3 in the morning to 10 or 15 or more during the day. There is aching in the back, and at times sudden and intense desire to defecate. As the disease becomes chronic, loss of weight is progressive, and finally marked emaciation may result. The patient becomes anæmic and the muscles soft; the tongue is pale and moist at first, later slightly furred, or sometimes heavily coated. There is more or less anorexia; indigestion and flatulence are common. The pulse and respirations may be slightly increased. The temperature is normal or subnormal in the morning and slightly elevated in the afternoon. As the malady progresses the anæmia becomes more marked, the skin dry and dull yellow in color, and the face drawn. The emaciation in some cases becomes very extreme; the abdomen becomes sunken, bed-sores may appear, and death follows from exhaustion or terminal infections. Another type of the chronic form is that in which there is nothing more than an intermittent diarrhœa often alternating with constipation, and accompanied, usually, by slow but gradual loss of flesh. These patients sometimes remain in this condition for several years. Occasionally the parasites disappear and the more serious lesions heal, but the bowel never assumes again its normal condition. Where the destruction of tissue has been extreme, cicatrices form and a chronic catarrh always exists.

The course of amœbic dysentery is very variable and is not self-limited. The grave cases with acute onset may terminate fatally within a week or ten days in spite of all treatment. The mild and moderately severe ones may continue for many months before alarming symptoms appear. The occurrence of complications may terminate the infection in death or completely alter its course. If proper treatment is instituted many of the mild and moderately severe cases recover entirely, and the para-

sites disappear in a month or six weeks. Some of the chronic ones are completely restored to health in from three to six months. Occasionally amœbæ persist after all symptoms and sometimes the lesions themselves have disappeared. Complete recovery is sometimes doubtful owing to the fact that after many weeks of apparent cure patients may develop more acute symptoms; sometimes these represent fresh infection, but usually they are merely evidences of the outbreak of the original disease. Cases of this nature, unless treatment is pursued until complete recovery results, are apt to suffer with so-called relapses every few weeks or months until some grave complication develops and carries them off. Patients who do not recover under continuous local treatment for six or eight months are likely either to die within a year or linger on as incurable. Rarely does an attack end in spontaneous recovery after the dysentery has existed for a year.

Death may occur from the gravity of the intestinal lesions, from exhaustion in protracted cases, from severe complications, from a terminal infection, from intercurrent diseases, or from severe intestinal hemorrhage. The severity of the intestinal lesions and abscess of the liver are the most frequent causes of death.

Analysis of the Symptoms.—**Gastro-intestinal.**—Of these, diarrhœa is the most important, usually being intermittent in character, coming on abruptly, and subsiding in like manner. Between the attacks the stools may become formed. The intermissions of the diarrhœa may last several weeks or even months, or this symptom may be absent throughout the entire course of the infection. The character of the diarrhœa usually depends, *first*, upon the ulceration, whereby increased peristalsis results, probably owing to the nerves being eroded and exposed; *second*, upon the impaired power of absorption of water by the intestine, due in part to the marked œdema. Ulcers of the intestine can exist without any diarrhœa, as is particularly likely when they are superficial and in the cæcum or the adjacent portion of the ascending colon. When the ulcers are very numerous throughout the intestine, or well developed in the descending colon and rectum, diarrhœa is practically always present. In mild cases the movements may not exceed 3 or 4 in twenty-four hours, but in the gangrenous and diphtheritic forms the diarrhœa becomes excessive and the movements sometimes number 50 or more in this time. In fatal cases before death they may diminish to 2 or 3. This has been explained as due to the gradual loss of expulsive power caused by the destruction of the muscular coat and nerves situated in the ulcerated areas, and the general œdema of the bowel wall.

The Fæces.—The stools vary greatly in different stages of the infection and in different cases. Valuable information may be obtained from them of the condition of the lesions in the intestine and of the progress of the disease. At times they are liquid, at times pultaceous, and again well formed. In color they may be brownish, greenish, reddish, grayish or variegated. In those cases with gradual onset they are likely at first to be merely more or less watery and of normal color. As the lesions develop, mucus begins to appear. In the cases with marked intestinal catarrh and extensive ulceration it is always more abundant. The mucus may be finely divided, shreddy and mixed throughout the stool, or it may appear in large masses. The latter condition is particularly likely to

exist when the fæces are well formed, when small portions of blood-stained mucus may be observed over the surface of different portions of the stool. At times the movements may consist almost entirely of viscid masses of blood-stained mucus.

Blood may be present so that the color of the whole mass is modified, or as clotted masses in portions of the stool, or mixed with mucus. It is sometimes in such small amounts as to be apparent only upon microscopic examination; or the stool may consist entirely of blood mixed with mucus. It is probable that the amount of blood is partially dependent upon the rapidity with which the lesions are forming as well as upon their position and extent. The presence of considerable blood in the stool makes the diagnosis of ulceration very probable; but we cannot conclude in its absence that ulcerations do not exist. When the ulcerations are high up in the cæcum the blood is apt to be altered and brownish or even blackish in color.

Pus cells are found chiefly after ulceration is well developed and in the diphtheritic form of the disease. In the chronic cases it is not unusual to find large numbers of polymorphonuclear leukocytes. These are to be distinguished from the small round cells so abundant where a well-developed catarrhal condition exists and where epithelial cells are also numerous. When pus is found in considerable amount it is an almost certain indication of extensive ulceration. The pus is frequently found only in small amounts.

Shreds of Tissue.—As ulceration advances and becomes more chronic the amount of blood grows less; the stools become more copious and again more watery; fragments of tissue are frequently seen in the early stages of the chronic cases. In advanced and particularly in gangrenous cases large sloughs and sometimes complete moulds of the intestine are cast off. These are of a grayish or brownish color and have a very offensive odor.

The reaction of the stools is generally alkaline, sometimes neutral, and occasionally acid. In instances of recovery the mucus is the last abnormal element to disappear from the fæces. It usually persists for a long period and in many cases where chronic catarrh remains it never disappears.

Microscopic examination reveals the amœbæ in addition to those elements which have been described. These may be very plentiful or scarce, the number depending upon several factors. If there are only a few ulcers in the large intestine the mucus and fæces that have come in contact with these lesions are likely to contain the parasites in the largest number, and they will probably be scanty elsewhere. If the stool is liquid the organisms will be more or less evenly diffused throughout. The gravity of the lesion is not always indicated by the number of amœbæ found. With very advanced lesions where the parasites are burrowing deep in the submucosa there may not be as many as in more acute conditions. In some instances blood can only be recognized microscopically. Numerous epithelial cells, small round cells, pus cells, eosinophiles, and a fair number of Charcot-Leyden crystals, are also frequently found. The bacteria are usually increased in number beyond those seen in normal stools.

Abdominal Pain.—This is very variable and occurs more acutely in the gangrenous cases and where perforation is imminent. It may be

colicky in character and very severe; localized over a particular ulcer, or exist over the abdomen generally. In chronic cases a dull aching pain with occasional sharp exacerbations may be present. When this is constant, limited to a fixed point, and increased by external pressure, it is suggestive of the site of ulceration, though the most extensive ulceration may exist without any pain whatever. Pain which is produced only by external palpation and pressure suggests areas of circumscribed peritonitis. Very excessive pain on pressure is usually present when the serosa itself is involved. If widespread or extensive ulcerations are present, pain on pressure may be elicited along the whole course of the large intestine. Cramp-like and aching pains frequently occur before and after evacuation of the bowel. A feeling of abdominal heaviness is not an uncommon symptom and is frequently accompanied by distension and flatulence. *Tenesmus* is not nearly so marked or frequent a symptom in uncomplicated amœbic dysentery as in the bacillary form. It is most evident in the grave cases and in the gangrenous and diphtheritic forms, where the sigmoid flexure and rectum are involved. In the remaining cases it depends chiefly upon the extent of the ulceration in the rectum. A burning sensation in the anus after defecation is frequently present.

Nausea and vomiting of severe grade are somewhat rare symptoms. They may occur early in the cases with acute onset. In moderate form they are most commonly encountered in the chronic ones. Nausea sometimes develops in all classes of cases as a result of the large and high intestinal enemas administered for treatment.

Loss of appetite is a common symptom and is almost absolute in the acute cases. In the moderately severe ones it may not be apparent, but it becomes very evident again in the chronic cases.

Hiccough is seen in the grave forms shortly before death and when the peritoneum is involved. The *tongue* shows nothing that is characteristic. In instances of very long standing it is likely to become fissured and to show small hemorrhages and erosions along its sides and tip.

Anæmia of a secondary type is present in all the cases of long standing and is progressive with the disease. It is dependent chiefly upon the loss of blood from the intestinal lesions and the gastro-intestinal disturbances. It is possible that it may be in part of toxic origin due to absorption. The reduction in hæmoglobin is usually greater than that of the number of the red cells; the hæmoglobin varies generally from 50 to 80 per cent. Fitch's average for the red cells in 38 cases was 4,802,000. In the tropics, in the advanced and chronic cases, the red blood cells sometimes are not over 2,500,000. There is frequently a slight leukocytosis, and if a marked one exists it is the polymorphonuclear cells which are increased. The eosinophiles are not increased in cases uncomplicated with other intestinal parasites.

Skin.—The skin is normal in the mild and moderately severe cases. In the chronic ones it becomes dry and sometimes glazed, and assumes a sallow, dirty yellow appearance when the mucous membranes show distinct pallor.

Fever.—The temperature is likely to be elevated in the cases with acute onset; it is generally higher in the diphtheritic form, and particularly when complicated with *Bacillus dysenteriae*. In the mild and moderately severe types there is usually little or no fever. In the chronic

ones the temperature is frequently subnormal for a portion of the day with afternoon rises to 100° to 102° F. At other times it may be subnormal or normal for a period of a week or more. In cases where there are many streptococci in the stools and advanced lesions of the intestine, it may become septic with daily rises to 103° to 104° F. Fever becomes an important symptom in perforation and in abscess of the liver and lung, when it is sometimes accompanied by rigors and sweating.

The pulse and respiration are apt to be increased if fever is present. The pulse is frequently rapid in the grave cases with acute onset, and may become thready and rise to 120 to 140 or more. Usually in cases of moderate severity it is not over 100, and in the mild and chronic cases it may be normal. The respirations are increased particularly in abscess of the liver and lung.

Urine.—Moderate albuminuria accompanied with a few hyaline casts is occasionally seen in chronic cases. The urine is then usually somewhat reduced in amount. Harris noted that in the severe forms the chlorides are often diminished and that in the most severe instances they may be entirely absent. Retention sometimes occurs when acute symptoms of dysentery are present.

Complications.—Abscess of the Liver.—This is the most frequent and one of the most serious complications. In 119 cases reported by Futcher it occurred in 22 per cent.; in a series of 100 cases examined at autopsy by Musgrave and the writer in 23 per cent.; in 74 by Craig, 33 per cent.; in 57 by Kruse and Pasquale, 11 per cent.; in 95 by Harris, 15 per cent. It is much more common in males than in females. Futcher reports 3 cases in the latter sex. The writer has not seen a case in a woman in the Philippine Islands, and but 1 in a native of these islands. However, Major E. C. Carter states that he has seen 1 case in a woman here and 3 cases in Filipinos. Rogers has shown that it is not uncommon in the natives of India.

Harris and others state that this complication always arises during the acute period but observations show that it may develop at any time, and certainly not uncommonly after all symptoms of dysentery have ceased, or indeed, sometimes before any intestinal ones have developed. One patient here first showed symptoms of abscess of the liver after five months local treatment for amœbic dysentery. Futcher's statistics show that it may appear at other times than in the very acute stage. However, in the majority the abscess became evident in the first month after the onset of the dysentery. The most common seat of the abscess is in the upper and posterior portion of the right lobe. Out of 639 cases of abscess in amœbic dysentery collected by Rouis, 70.8 per cent. were situated in the right lobe and 13.3 per cent. in the left lobe. There may be single or multiple large abscesses or very numerous small ones scattered throughout. In Futcher's series out of 18 cases, 10 were single. In the writer's series, 13 were single and 10 multiple. In Craig's, 9 were single and 15 multiple; and in Rogers's, 21 single and 11 multiple. The number of abscesses is obviously an important factor from a surgical standpoint.

For a long time alcohol has been believed to predispose to liver abscess and play an important part in its etiology. In 12 cases among private patients, 8 were alcoholics. In these islands at least, malaria is generally

not a predisposing factor. Kartulis has reported 6 cases of liver abscess with amœbic appendicitis. In 3 the intestinal lesions were most marked in the cæcum and appendix. In 1 the appendix was most extensively diseased while in the cæcum only 3 small ulcers existed. He suggests that the portal of entry of infection may sometimes be through lesions in the appendix.

The amœbæ are supposed to reach the liver by two paths. The more common is certainly through the portal vein. Amœbæ are frequently found in the veins of the submucosa and in the portal capillaries. The other method of transmission is through the peritoneal cavity. Councilman and Lafleur, and Rogers all support this theory and think that infection occurs in many cases in this manner. The parasites are supposed to migrate through the intestinal wall and then invade the liver from its surface. Lafleur has cited an instance with peritonitis present in which amœbæ were found over the peritoneal surface of the intestines and liver. This would certainly seem to be one mode of infection. In one of the writer's cases an amœbic abscess occurred beneath the right rectus muscle, the infection apparently having entered through the parietal peritoneum. In another the abscess was less than a centimeter in diameter, solitary, and occurred just beneath the surface of the right lobe of the liver.

Bacteriology.—In addition to amœbæ the abscesses are usually infected with bacteria. In 27 cases reported by Fitcher and examined bacteriologically, 15 contained bacteria; of the writer's 23 cases bacteria were found in 13, and in 37 of Rogers's they were present in 16. In the larger abscesses the bacteria may have died out, but a proportion of even the earlier abscesses seem to be entirely sterile. The organisms most frequently found are the *Staphylococcus* and the *Streptococcus pyogenes* and the colon bacillus; the *Micrococcus lanceolatus* and the *Bacillus pyocyaneus* have occasionally been reported. It is obvious why bacterial infection occurs so frequently, as these organisms have the same opportunity for entering the liver as the amœbæ and frequently adhere to them. Undoubtedly the pus cocci exert an injurious influence upon the hepatic tissue, but there can be little doubt that the amœbæ play a most important part in the formation of the abscess. This is demonstrated by the very different character of the amœbic and the pure bacterial variety. The contents of the former vary somewhat. In the smaller abscesses they consist of thick, glairy, yellowish masses of mucus which are not fluid. In the large abscesses the contents are more liquid, frequently like thick gruel, and yellowish, grayish-red, brownish-red, or at times greenish in color. Frequently shreds of necrotic liver tissue are mixed with the fluid portions. Microscopically one is struck usually with the absence or presence in small numbers only, of polymorphonuclear leukocytes. The contents consist mainly of fine or more coarsely granular material containing fragments of cells, many swollen and fatty degenerated liver cells, red blood corpuscles, fat globules, and amœbæ. The latter are sometimes difficult to find in the pus, but can almost invariably be obtained in scrapings made from the abscess wall, though sometimes repeated examinations are necessary to detect them.

Special Pathology.—The liver may be of normal size, but is frequently enlarged. The tissue often shows advanced fatty degeneration or chronic

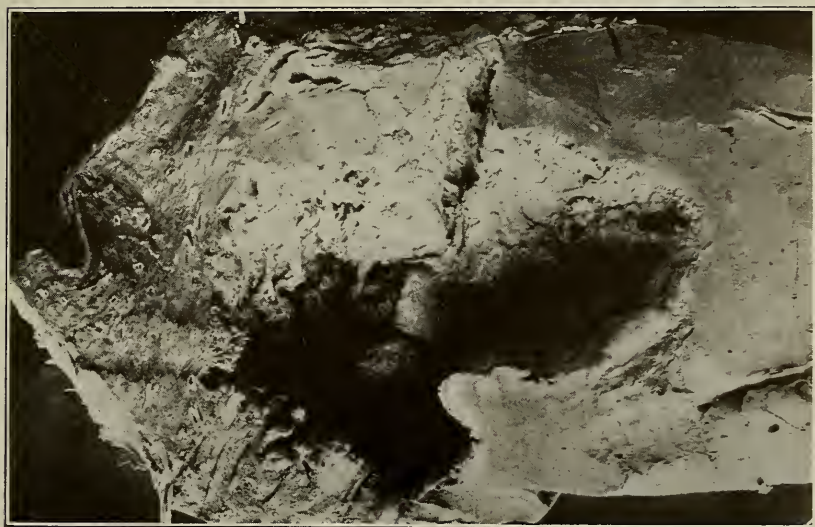
PLATE VIII

FIG. 1



Large Single Amœbic Liver Abscess.

FIG. 2



Hepatopulmonary Amœbic Abscess

passive congestion, or, sometimes, it is acutely congested. There are areas of localized peritonitis where the abscesses reach the surface of the liver, and the overlying tissues may then be bound by adhesions to it. The size of the abscesses may vary from several millimeters in diameter to that of a man's head. In one of the writer's cases a single abscess occupied the entire right lobe, only a shell of liver tissue remaining. The liver and abscess weighed 3,700 grams. Very frequently several abscesses about the size of an orange are encountered. A somewhat rarer condition is that in which very numerous small abscesses are scattered throughout both lobes of the liver. When the contents are evacuated the walls of the small ones generally show a sharp contour. Those of the larger ones have an uneven and ragged necrotic appearance. The liver tissue along the margin of the abscess is softened and infiltrated. The older abscesses usually have walls composed of a dense layer of fibrous connective tissue. A microscopic study of the periphery of the small abscesses shows that the interlobular areas are always the first to become disintegrated, and to this is due the irregular contour, the periportal areas persisting until detached by the interlobular necrotic processes. The edge of the abscess consists of a necrotic area of liver cells where the amœbæ, together with leukocytes, blood corpuscles, and fibrin filaments, are frequently found. The capillaries are dilated, filled with blood, and frequently contain the parasites. The latter show no indication of attempting to penetrate beyond the necrotic zone. Outside this layer is a zone in which great activity of the connective tissue cells is observed and in which the liver cells are frequently compressed and atrophied; mononuclear small cells are usually abundant. Finally this layer is usually surrounded by a zone of more marked hyperæmia where small hemorrhages are frequently found. In these latter areas thrombi may occur in the branches of the portal veins, where amœbæ and bacteria may both be found. Councilman and Lafleur, in addition to the abscess formation, have also described a widespread necrosis of the cells situated round the central veins of the lobules and scattered throughout the liver. They suggest that this is due to soluble chemical products of the amœbæ. A striking point also observed in the hepatic lesions is the absence of leukocytic infiltration, which usually accompanies suppuration of bacterial origin. (Plate VIII, Fig. 1.)

Diagnosis and Symptoms.—Liver abscess is frequently overlooked, and this is not strange, for sometimes its development takes place so insidiously that perforation may be the first indication. If the onset is more acute the diagnosis is simplified. Pain is very common at some time. It is commonly dull and aching but may become sharp and lancinating. Its situation varies greatly, being almost as frequent in the vicinity of the right scapula and shoulder as over the liver itself. In the former case the pain is, according to Fletcher, reflex through the phrenic nerve which receives large branches from the fourth cervical. The pain may occur over the hypochondrium or epigastrium. When not present spontaneously it may be elicited upon pressure over the liver. However, pain is not constant, and is frequently absent. Fever is usually present at some time, but is often not sufficient to attract attention. Occasionally it is continuous and not over 100° to 102° F. In other cases it is remittent; or it may be septic in type and intermittent and rise in the evening to

104° F. Chills and sweats may then occur, and the symptoms simulate those of malaria. Lafleur calls attention to sweating as an important symptom, and states that it is independent of the temperature. The pulse may be little increased, but in the cases with high fever it may be 140 or more.

Blood.—There is usually a leukocytosis from 15,000 to 40,000 in which the polymorphonuclear cells are increased. However the leukocyte count may be normal.

The conjunctivæ are sometimes slightly tinged with yellow, but marked jaundice is rare. Persistent vomiting may occur. The skin frequently assumes a sallow color; and the face may become pale and yellow. The facies may suggest the diagnosis. In certain cases emaciation occurs rapidly; in others the flesh is well retained. The appetite usually disappears and the tongue becomes coated. Physical examination may show enlargement of the liver which may even cause bulging on the right side; pain may be elicited on pressure. Occasionally a swelling may be observed over the sixth and seventh ribs. Percussion and auscultation frequently give no information of the condition. If the abscess is large, percussion may reveal an increase in hepatic dullness. A friction rub may be heard over the liver when the peritoneum is involved. In the diagnosis of liver abscess there is not a single symptom that is constant, and proof that the liver is involved may be very doubtful. The general condition and appearance of the patient, with the progress of the case, rather than any single symptom, often suggest the diagnosis, which may sometimes be confirmed by aspiration.

Spontaneous rupture of amœbic abscess frequently occurs if the patient lives long enough and is not operated upon. This is most often into the lower lobe of the right lung. Rupture into the abdominal cavity causing general peritonitis is also frequent. The abscess may perforate into the pleura, pericardium, stomach, colon, small intestine, bladder, vena cava, kidney, and through the skin in the lumbar or right hypochondriac region.

Kartulis has reported brain abscess in 3 per cent. of his liver abscess cases. Amœbæ were found in the vicinity of the necrotic areas. Jürgens had 2 cases of thrombosis of the femoral vein, in 1 of which amputation of the leg was necessary.

Abscess of the spleen may occur.

Abscess of the Lung.—Preceding this, the respirations are usually increased in number and are often painful and shallow. Before perforation occurs the physical signs of pleurisy are usually present. Cough and expectoration then appear, and are generally constant. The cough in the early stage is hacking and accompanied by pain over the liver. When the abscess discharges into the pleural cavity or into a bronchus, the dyspnœa becomes less marked. Sooner or later the characteristic anchovy-sauce-like sputum appears, in which can be found amœbæ with red blood corpuscles, leukocytes, altered liver cells, alveolar epithelium, elastic tissue fibers, Charcot-Leyden, tyrosin and hæmatoidin crystals, and various bacteria. Small cheesy particles consisting of granular material and oil drops are also encountered. (Plate VIII, Fig. 2.)

Special Pathology.—In abscess of the lung the diaphragm is adherent to the liver and usually to the base of the lung. If the latter is not the case, a layer of pus separates the lung from the diaphragm. Abscesses

are never metastatic, and the lower right lobe is always the one affected. The diaphragm may or may not be visibly perforated. On opening the lung abscess it may be found filled with viscid yellowish-gray or yellowish-red partially fluid material; or, if perforation into a bronchus or the pleural cavity has occurred, it may be empty. The walls of the abscess are frequently more uneven than those of the liver abscess; in places, however, they may be smooth and formed of dense connective tissue. Sections of the older abscesses show usually three zones; first a necrotic one containing fragmented nuclei, degenerated cells, and amœbæ; second, a layer composed of connective tissue fibers, epithelial cells, elastic fibers, sometimes distinct groups of air cells, and occasionally amœbæ; and third, a layer of small round-cell infiltration in which fibrin and some proliferation of the connective tissue fibers is also visible between the air cells. The walls of the bronchi are thickened and infiltrated with numerous round cells. The bronchi contain either purulent or serous fluid.

Hepatopulmonary abscess is a somewhat rare condition. Harris reports it 3 times in 95 patients, and Fitcher 9 times out of 119 with 3 cases in which the liver abscess ruptured into the pleural cavity. In the writer's series of 100 fatal cases, hepatopulmonary abscess occurred but once with 2 cases of empyema. Perforation of the liver abscess into the lung does not always occur. The extension may result through the diaphragm without visible perforation. When rupture into a bronchus takes place, the condition may last from six to eight weeks and terminate in death or recovery, or persist for a year. The mortality is usually very high.

Peritonitis.—A local peritonitis may result from extension of the ulceration in the bowel or from an abscess in the liver. Patches of fibrous adhesions are of very frequent occurrence; in chronic cases it is the rule to find old localized areas of chronic adhesive peritonitis. These are very difficult to diagnose during life. They may cause abdominal soreness and pain. Peritonitis, which generally proves fatal, may follow perforation of a liver abscess or an intestinal ulcer.

Perforation.—Perforation of the intestine results generally from the giving way of the base of a deep sloughing ulcer and is most frequent in the grave and gangrenous cases. The opening is usually a large one. The perforation occurs frequently in the cæcum, and the condition has sometimes been mistaken for one in which the appendix is involved. Perforation of the large bowel with general peritonitis occurred in 19 of the writer's 100 autopsies. In 2 other cases it occurred after the ulcer was thoroughly walled off from the peritoneal cavity. In Fitcher's series, perforation occurred only in 3 and in Craig's in 4 cases. In the writer's series of 200 clinical cases it occurred but 3 times. It is almost invariably fatal. In one of the Johns Hopkins series the patient was operated upon three hours after the perforation occurred, but died. Death may occur in a few hours from shock, or later from the resulting acute general peritonitis. Perforation sometimes happens after adhesions have formed, when a pericæcal or pericolic abscess may result. It may take place retroperitoneally into the psoas muscle and may even open externally.

Appendicitis.—This complication occurred in 7 of my 100 fatal cases. In one a chronic appendicitis existed in connection with a pericæcal

amœbic abscess In 4 of the 6, death resulted from general peritonitis following perforation of the cæcum or colon. All showed extensive general intestinal lesions and the involvement of the appendix merely followed extension from the cæcum. A definite diagnosis of the appendicular affection during life is very difficult since the cæcum in addition is usually extensively diseased. The process is not very acute as a rule. It consists of the formation of ulcerations in the walls of the appendix. In only one of the writer's cases was the appendix perforated at its tip.

Intestinal Hemorrhage.—Intestinal hemorrhage in which large amounts of pure blood are passed from the rectum is a rare complication. Councilman and Lafleur report but 1 case in which 125 Cc. of blood were passed. Death was apparently due to the bleeding. In 1902, the writer called attention to severe intestinal hemorrhage as a fatal complication and reported 2 cases in both of which liver abscess was present and in which death was due to severe multiple hemorrhages. It was suggested that these large hemorrhages might perhaps bear some relation to the condition of the liver. Shortly afterward Haasler reported from China 3 more instances of intestinal hemorrhages, in 2 of which death took place from bleeding. In both of these cases liver abscess also existed. Since this time the writer has seen 2 more fatal cases from multiple hemorrhages, both with liver abscess, and therefore a connection between intestinal hemorrhage and the hepatic condition is suggested. While it is probable that fatal intestinal hemorrhage in amœbic dysentery may occur independently of liver abscess, the cases mentioned suggest that when hemorrhage occurs in patients with liver abscess it is likely to be very severe, and the bleeding is likely to recur. Futeher reports intestinal hemorrhage in 3 of his series. Why is severe intestinal hemorrhage not more frequent in amœbic dysentery? One should consider the following points: the thrombosed condition of the bloodvessels in the zone of infiltration and the œdema which surrounds the ulcers, the infiltration of the walls of the arteries and the more or less marked evidence of endarteritis as the progress is rapid or slow. In chronic cases one may see at times the arteries entirely occluded by this process.

The frequent occurrence of small amounts of blood in the stools may be explained from the fact that the walls of the veins are early infiltrated with round cells, followed by softening and complete disorganization, also from the fact that amœbæ may penetrate the walls of a vein. However, thrombosis of the veins is not infrequent.

Sequelæ.—In old chronic cases with extensive ulceration large cicatrices frequently form. When a long-continued catarrhal condition has been present a general atrophy of the mucosa may take place. In these instances we sometimes find a clinical condition closely resembling *sprue* or *psilosis*. The small intestine, owing to the inanition, anæmia, etc., may also become secondarily involved and its mucosa atrophied. The stools then are copious, liquid (at least never formed), pale in color, and usually frothy. The chronic gastric catarrh and enteritis, which frequently develop with a sore and fissured tongue and often an inflamed œsophagus, complete the picture. This condition was observed in 3 very chronic patients who finally overcame the amœbic infection.

Diagnosis.—This is not difficult by microscopic examination; but there are other forms of dysentery which clinically it may be impossible

to distinguish from the amœbic variety, and any one who attempts to make a diagnosis from the clinical manifestations alone will make frequent mistakes. The occurrence of amœbic liver abscess always confirms the diagnosis, but sometimes the symptoms to which it gives rise are the first ones to attract attention to the intestinal disease. The examination of the stools should be made as soon as possible after they are passed, and the specimens should be collected free from urine. Many observers recommend in cold climates that a warm bedpan be used and that the microscopic slide be gently warmed. This is not necessary in tropical countries. These precautions are necessary because the amœbæ frequently die in stools that have stood for any length of time or that contain urine, and their motility is often quickly impaired by cold. The amœbæ must be found living and motile. In this condition they are easily recognized and cannot be mistaken for other bodies. After movement ceases and death or encystment results, it is frequently impossible to distinguish them from other substances. It is necessary to emphasize that the amœbæ must be motile, for upon the presence of such forms depends the diagnosis of the disease. Usually the examination of several specimens from one stool reveals the parasite, but sometimes the study of several upon different occasions is necessary. If bloody mucus or small pieces of necrotic tissue are present, these should be examined first, for if they come from the neighborhood of an ulcer they usually contain very large numbers of amœbæ. If the movements are not liquid a dose of Rochelle salts should be given and the fluid portion of the stool examined. Another very convenient method of securing material for examination is by the passage of the rectal tube. When the stools are fluid considerable amounts may be obtained, or small portions of mucus will be found in the lumen of the tube.

Since Schaudinn insisted upon the harmlessness of *entamœba coli* for man it is important to distinguish between this and *entamœba histolytica*. For differentiation Lesage has recommended the addition of a dilute watery solution of iodine to the fluid stools. This brings about in a few minutes encystation by which the amœbæ may be distinguished from one another. However until we know more about *entamœba coli*, in any instance in which symptoms of intestinal disturbance exist and amœbæ are found, the diagnosis of amœbic colitis had best be made and the proper treatment instituted; for, in an intestine with erosions, probably the *entamœba coli* may cause additional disturbance from its mechanical movements, even if it is not capable of producing any other pathological effect. If, however, one chooses to attempt the separation of the two forms by their pathogenic action, extensive animal experiments, preferably upon cats, must be performed with the parasites found in the stools. Infection with other disease may co-exist, and in cases with acute onset it will be important and advisable to make plate cultivations of the bacteria from the stool and search for *Bacillus dysenteriae*, as well as test the agglutinative and bactericidal reaction of the patient's blood serum with this organism.

The diagnosis of liver abscess should be made only after a careful consideration of all the existing symptoms. The general condition of the patient and his fæces together with the progress should be taken into account. The blood should be examined to exclude malaria and for a

leukocytosis, but it must be remembered that the leukocyte count may occasionally be almost normal. If no intestinal disturbance exists, an additional clue may be obtained from the history or by finding the amœbæ in the stools. An absolute diagnosis can frequently only be made by the finding of amœbæ in the abscess. This may sometimes be done by aspiration before spontaneous evacuation or operation. This should be done with a needle having a sufficiently large caliber to transmit the thick pus. The puncture may be made through the skin, the point of entrance being over the suspected area; but the surgeon must be at hand to operate if necessary. The method may fail and if unsuccessful should be repeated. When pus is obtained it may contain no amœbæ, but the absence of large numbers of leukocytes and the presence of much granular material will suggest that the origin is amœbic.

The diagnosis of amœbic hepatopulmonary abscess may be definitely made when the patient suddenly begins to expectorate quantities of reddish brown anchovy-sauce-like sputum containing liver cells, hæmatoidin crystals, and amœbæ. The latter are always present, though sometimes a prolonged and repeated search is necessary to find them.

Prognosis.—There is no doubt of the gravity of the disease and when well advanced before proper treatment is instituted the final outlook is often doubtful. The symptoms in the majority of cases yield to treatment in a short time and the patient may feel quite well. It is in this condition (when he falls into the hands of those not thoroughly familiar with the malady) that he is frequently discharged only to return sooner or later with a recurrence. This may happen a number of times, and among this class of patients the mortality is always high. In untreated patients who are exposed to hardships, the death-rate is very great. Out of 78 collected cases (Harris) in the United States there were 30 deaths. In the Johns Hopkins series of 119, 28 terminated fatally; however in both of these series it seems probable that many were well advanced before treatment was instituted, since patients in America do not as a rule enter hospitals in the earlier stages of the disease unless the symptoms are severe. One might expect a somewhat different outcome if treatment were instituted early.

In the writer's series of 200 treated cases, which included all stages of the disease and from which accurate data were obtained, there have been 12 deaths and 4 are chronic invalids; the remainder have recovered. Tuttle has recently reported 73 cases in the United States with 70 recoveries. In children the prognosis is almost always good. Amberg and Musgrave each report 1 death. Adding together these cases we have 44 cases in children with 2 deaths, a mortality of 4.5 per cent. In the uncomplicated cases, those with acute onset, including the gangrenous form, usually have the gravest outlook. The writer cannot agree with Lafleur that a mild onset is no indication of a favorable course, for when local treatment is instituted early these cases usually progress favorably.

In liver abscess the outlook is always very grave. Fitcher reports 19 deaths out of 27 cases; 17 of these were operated upon but only 5 recovered. In the writer's clinical series of 200, abscess of the liver occurred in 12, 3 of whom recovered after operation. The prognosis when hepatopulmonary abscess exists is perhaps even graver.

Immunity.—While in many instances there seems to be a natural resistance to the disease, it would appear doubtful if there is any acquired

immunity against it. The apparent natural resistance may depend upon the fact that the parasites are killed before reaching the large intestine, or that they do not find favorable conditions for life and reproduction. The amœbæ, after the development of the disease, may disappear from the stools independently of treatment, but this may be brought about by unfavorable conditions in the intestine rather than by any acquired immunity. Our knowledge of immunity in amœbic dysentery amounts to almost nothing. Perhaps further light may be thrown upon it from the study of the secretory products of the parasites, their enzymes, endo and soluble products, etc., as well as by the application of other methods which have been employed in the study of immunity in bacterial diseases. Work of this nature has already been commenced in the laboratory in Manila.

Treatment.—Prophylactic.—Since the disease is only acquired by the ingestion of the amœbæ in food or drink, it is a preventable one, and may be avoided even when the malady exists endemically. Drinking water is the most usual medium, and hence only that which has been sterilized is safe to use. A reliable bottled imported aërated water is the safest to use in localities where the general water-supply is infected. Salads and uncooked fruits are sometimes a possible means of conveyance and should be avoided unless prepared with great care, particularly since they also may be a source of infection with other intestinal parasites.

General, Dietetic, and Symptomatic.—Patients with acute onset or acute exacerbations of the disease should be confined to bed. In the most severe forms when very frequent bloody mucous stools are being passed, the diet should at first consist of nothing but rice or albumin water. Later milk may be added. Rest is most essential, and for this hypodermic injections of morphia sulphate (gr. $\frac{1}{4}$, gm. 0.016) may be given every three or four hours. Its use should be pushed if necessary. Local treatment in this stage is contra-indicated. The essential point is to secure rest for the patient and for the acutely inflamed bowel. If this can be accomplished the condition usually improves. As the symptoms begin to abate, Dover's powder (gr. 10, gm. 0.6) may be substituted for the morphia. This should be continued until the acute symptoms have subsided, when local treatment may be commenced. If the patient be seen before the symptoms are very acute a saline purge may be given, but if the severe symptoms have set in this is contra-indicated. In the mild attacks and those of very moderate severity it has become the custom in Manila not to confine the patient to the house but to allow him to be about and to enjoy a liberal diet. There is no doubt that this is frequently a mistake, but as the majority of these do not feel ill, they also feel that they are unable to remain away from their work and take the advised rest. Many of them it is true are better off when not confined to bed for the reason that they are likely to retain their strength better when up; but rest at home is usually advisable, though an occasional drive in the afternoon is often beneficial for its general effect.

Where any intestinal irritation exists the diet should be restricted. Fresh milk, when obtainable, should be chiefly employed. It may be necessary to peptonize it, and this should be done if curds appear in the stools. If it is not well borne, other liquid nourishment may be substituted. It is of course advisable to feed the patient frequently and in

small quantities. As the symptoms improve, other liquids and soft food may be gradually added. Not until the stools appear perfectly normal should general diet be permitted. Any lesions of the intestine will certainly be more disadvantageously affected by solid than by liquid food.

Nausea and vomiting are frequently very annoying symptoms. They may result from the treatment or be one of the results of the disease itself. The vomiting while annoying is very rarely persistent or continued. The alkaline carbonated waters will sometimes give relief, and strychnine sulphate may be employed in tonic doses. Pepsin, hydrochloric acid, and pancreatin are rarely of benefit. In some, sodium bicarbonate in combination with bismuth gives the best results.

The use of bismuth is not contra-indicated in the treatment of amœbic dysentery. Some writers have thought that it may interfere with the local treatment. This may be true where it is allowed to accumulate in the bowel. It occasionally is of service when diarrhœa persists, for by its use in one-dram doses every three or four hours constipation may be produced and a condition of the intestine brought about in which the amœbæ die out. Just why the parasites cease to multiply and to exist it is difficult to say. Obviously one must not be led away with the idea that because the diarrhœa has stopped the lesions are healed and the parasites have disappeared. Repeated examination of the stools must be made to ascertain if the amœbæ have really died out. Ipecac and opium may sometimes bring about the same results. In cases where bismuth is employed, a saline cathartic followed by a high rectal enema should be given at least once or twice a week.

In some instances of the disease an acute attack of diarrhœa has brought the patient for treatment. They have been confined to bed for a few days, several doses of Dover's powder administered, and local treatment instituted. The parasites may never be found in the stools after the first week, though numerous in the first examination. The symptoms will subside during this time and a recurrence does not take place. In other cases with identical treatment the parasites may persist for weeks or months. Certainly the destruction of the parasites in the former instance is not brought about by the direct action of the medicine administered by the mouth, nor is their early disappearance probably always dependent upon the direct action of the quinine administered in the enemata. The only explanation is that in one instance conditions in the intestine unfavorable to the life and propagation of the amœbæ are brought about, and in the other we fail to produce them.

Abdominal pain may be very troublesome. It may be relieved by turpentine stupes and hot fomentations; or, if severe, opium may be administered. When ulcers exist in the rectum and there is much tenesmus, local treatment with argyrol or some other astringent or antiseptic substance may be applied through the speculum after the administration of a small enema containing cocaine or morphia. Enemas of starch and opium sometimes have a very soothing effect. If the anæmia is advanced some iron preparation is necessary; and when there is much lassitude and anorexia, a course of strychnine and alcohol in moderation is often of value. A change of climate is frequently beneficial during convalescence, and patients who after a long time seem to make no progress in the tropics are often improved by a bracing cool atmosphere.

Curative Treatment.—During the writer's first year in the Philippine Islands he employed ipecac, and saw it used extensively, but concluded that it is not in any sense curative, and that, probably, the subsidence of the acute symptoms which sometimes takes place after its use is due more to the effect of the opium which is administered.

Intestinal antiseptics by the mouth have practically no effect upon the parasites in the large intestine, or over the course of the disease. Calomel in divided doses has many advocates. It may be employed with good results when the usual symptoms indicating its use appear; but has no definite influence upon the parasites in the intestine. When the patients have no stool except after the enema, or in cases with constipation, either small doses of calomel or a saline purge should be administered at least once a week. The administration of quinine by the mouth on account of the effect it may have upon the amœbæ in the tissues has been advocated, but its use in enemata seems to be equally, if not more, advantageous.

Local treatment by rectal injections and irrigations is by far the most efficacious. After employing many substances, the writer concluded that quinine solutions give the best results. A reservoir of a capacity of two liters is advisable, which during use should be placed at a height of four to five feet above the patient. The rectal tube should be at least three or four feet in length, and not so soft as to fold too easily, or too stiff as to be apt to injure the bowel in introduction. It should be covered with vaseline before use and introduced if possible its whole length. The fluid should be allowed to enter slowly and the hips should be elevated. The solution may be 1 to 5,000 or 1 to 1,000 to begin with, and after a few days should be increased to 1 to 500 and used continuously at this strength. The amount injected should usually be about two liters; some patients will be able to take more and some less. The enema should be retained if possible fifteen minutes, and at least five minutes. Difficulty may be encountered in giving these large injections, and in passing the rectal tube its whole length. The attending physician should, for a few days, either administer the enemas himself or have a trained assistant do so. The writer has never seen an accident result from this treatment. It is sometimes necessary when the rectum is very irritable to introduce a cocaine suppository first; or the irrigations may be suspended for a day or two.

Harris recommends hydrogen peroxide in preference to quinine, and nitrate of silver solution 30 grains to the quart, corrosive sublimate 1 to 3,000, benzoyl-acetyl-peroxide (acetozone), and disuccinyl peroxide (alphozone) 1 to 2,000; slightly acid solutions have also been recommended. Recently Tuttle has obtained very favorable results with ice-water, particularly when the temperature is below 45° F. Harris reported in his first paper that not in a single instance did improvement follow injections of ice-water.

One or two enemas daily are usually sufficient. In certain cases in robust individuals as many as three may be employed. A greater number than this will probably always do more harm than good. It is probable that the mere flushing out and cleaning of the colon plays an important role in the treatment, and many recover when saline solutions or ordinary water enemas are employed. It is obvious that this washing

out must not be performed too often or the general condition of the patient may suffer, and the mucosa itself be injured and healing delayed. There are a number of cases in which the parasites persist even after all symptoms have disappeared and we are not able to rid the patient of them by any known means. Every physician who carefully and repeatedly examines the stools of his patients before discontinuing the local treatment will find this to be the case. Still, in other instances the parasites appear to persist, chiefly owing to their burrowing in the sub-mucosa where we are not able to reach them by local treatment. In those cases in which the lesions have healed and the parasites still persist, the time to discontinue treatment is important. If it is decided to interrupt the treatment, the enemata should be gradually reduced to one or two a week before their complete withdrawal, and the stools carefully watched for blood cells or other evidences of intestinal disturbance. Of course the prolonged local treatment for several months usually brings about a catarrhal condition of the large intestine which may exist for a long time or never disappear.

In patients with suspected lesions in the cæcum which do not yield to treatment by the rectum, colostomy has been recommended, or the appendix has been drawn out and amputated and the irrigations given directly through the cæcum. The writer has seen only one advanced case treated by this method. The patient was not apparently benefited by it and succumbed about a month later.

Treatment of the Complications.—Abscess of the liver should be opened and drained as soon as the diagnosis is made, unless it has already perforated into the lung and is being freely discharged through a bronchus. If the abscess is opened it should be frequently irrigated with quinine solution. If it is not found or no operation is performed the medical treatment indicated is the usual one for septicæmia. Perforation of the bowel also demands surgical aid if the condition of the patient warrants it; there is practically very little hope of recovery, since in those cases which perforate the remainder of the bowel is so extensively diseased that the patient usually succumbs from the gravity of the lesions, or asthenia, if not from the general peritonitis. Morphia should be administered for the pain. Local peritonitis without perforation requires rest and the application to the abdomen of ice or hot fomentations, with opiates by the mouth. For serious hemorrhage, morphia should be given and ice applied locally to the abdomen. Ice-cold or hot enemata containing tannin, silver nitrate, or calcium chloride, may be tried in extreme cases. Stimulants and subcutaneous or intravenous injections of salt solution should be employed when their use is indicated.

PART VII.

THE ZOO-PARASITIC DISEASES OF MAN.

(EXCLUSIVE OF PROTOZOAN INFECTIONS).

CHAPTER XXIII.

GENERAL DISCUSSION.

By CHARLES WARDELL STILES, PH. D., D.Sc.

Nature and Kinds of Animal Parasites.—A parasite is any organism which lives in or upon any other organism, called the host, and generally belonging to a widely distinct species, at whose expense it derives its nourishment and habitation. Thus the prime ideas in parasitism are food and association.

1. Food.—No distinct line can be drawn between a parasite and a predaceous animal, although, as a rule, the parasite attacks organisms which are larger, stronger, and more intelligent than itself, and does not immediately kill and devour its host, while the predaceous animal attacks animals which are smaller, weaker and less intelligent than itself, and it kills and devours its prey.

2. Association.—Association of animals is one of the most common biological phenomena, and may occur between individuals of the same species or between individuals of different species. In the former case we usually have to deal with an association such as pairing (birds), or colonization (bees), resulting in a propagation and protection of the species, and a higher specialization of structure, but rarely with parasitism. In the latter case, however, when organisms of different species associate together, we rarely have to do with partnership for the purpose of propagation (hybrids), but usually with a case of parasitism, involving a specialization but degradation in structure. Such association may present an instance of—

(a) *Mutualism*, when the partnership results in benefit to both parties, as in the case of the sponge growing on the back of a crab, or in the case of some of the bacteria in the mouth; or

(b) *Commensalism*, when the association results in a benefit to one party (the messmate), but neither benefit nor injury to the other (the host), as in the case of the non-pathogenic *Entamæba coli* (not *E. histolytica*) in man; or

(c) *True parasitism*, when the association results in a benefit to the parasite, but an injury to the host, as in the pathogenic *Entamæba histolytica*, or trichinæ, hook-worms or the tapeworms in man.

A parasite may visit its host only at intervals to take up temporary residence and to obtain food; such animals (mosquitoes, bed-bugs, etc.), are called *temporary* parasites. Others are more or less stationary with their hosts, and are therefore called *stationary* parasites; of these, we may have *periodical* parasites, which spend a given period of their life with their hosts (as bots under the skin, or *Strongyloides stercoralis* in the intestine of man), or we may have *permanent* parasites, such as trichinæ, in which the entire life-cycle is parasitic.

Some parasites, as the pinworm, eelworm and hookworm, require only one host to complete their life-cycle; others, such as the large tapeworms, require two hosts—an *intermediate host* in which the larval stage lives, and a *definite or final host* which harbors the sexual stage.

All cases thus far cited are examples of *simple* parasitism, but we may have parasites which are parasitic in or upon other parasites, a phenomenon known as *hyperparasitism*, and important from an agricultural point of view.

We may further have *ectoparasites* (as lice), which live upon animals, and *endoparasites* (as tapeworms), which live in animals. The term *entozoa* refers primarily to the *endoparasites*, and *helminthes* refers especially to the parasitic worms, while *helminthology* is that part of zoölogy which deals with worms, especially the parasitic forms, and *helminthiasis* denotes an infection with parasitic worms.

Chance parasites, or *pseudoparasites*, are animals which are usually free-living but are, by chance, living as parasites (as the vinegar eel in the human bladder, mosquito larvæ, and *Gammarus pulex* in the stomach), or parasitic animals which by chance are not in their normal host (as *Fasciola hepatica* in man).

Spurious parasites are objects which are described as parasites or mistaken for such, but which in reality are creations of the imagination (*Furia infernalis*, *Uermis umbilicalis*), or half-digested food (*Diacanthos polycephalus*; *Striatula*; banana cells mistaken for tapeworm segments, etc.), or objects introduced into the body by hysterical patients in order to confuse the physician (frogs, earthworms—*Spiroptera hominis* is a parasite, *Ascaris capsularia* of fish, introduced by a girl into her vagina to confuse her physician, etc.).

Frequency.¹—As a general rule, the smaller a parasite is, the more individuals there may be in a patient; compare, for instance, *Tænia saginata*, *Ascaris lumbricoides*, *Oxyuris vermicularis*, *Entamæba coli*, *Giardia duodenalis*.

There is no species of animal, and no race or class of man known to be free from parasites. We may, however, lay down certain general rules covering the frequency of infection:—

1. Certain parasites are more common among people of careless personal habits than among those of more careful personal habits; thus, as a rule, dwarf tapeworms, eelworms, and pinworms are more common in

¹See also, Stiles and Garrison, 1906 a, pp. 1-77, "A Statistical Study of the Prevalence of Intestinal Worms in Man." *Bulletin* 28, *Hygienic Laboratory U. S. Public Health and Marine Hospital Service*, Washington.

children than in adults, and whipworms are more common in negroes than in whites.

2. Certain parasites (eelworms) are said to be more common among people who—as in villages—drink unfiltered water than in townspeople who have a filtered water-supply. The difference in frequency is influenced, however, by the disposal of feces by a better sewage system in cities than in villages.

3. Certain parasites (trichinæ, pork tapeworms) are likely to be more common among people who (as East Prussians and Saxons) eat raw or rare pork than among people who (as South Germans, French, Americans) eat their pork well cooked.

4. Certain parasites (hydatids) are more common among people who (as in Iceland) keep large numbers of dogs and live more intimately with them, than among people who keep fewer dogs in proportion to the population.

5. In general, animal parasitism increases from temperate to tropical climates.

6. All intestinal and some hepatic parasites decrease hand in hand with the increase of care exercised in a proper system of latrines or sewers.

Age and Sex of Patient.—Some parasites (eelworms, pinworms) are more common among children, while other species (large tapeworms and hydatids) are more common among adults of from twenty to forty years of age; some parasites (large tapeworms, hydatids, head-lice) are more common among women than among men, while other species (lung-flukes, pubic-lice) are more common among men.

Fertility of Parasites.—Most parasites are exceedingly fertile, some of them almost representing egg-machines. This fertility is:

1. A natural result of their environment, since they live in the midst of their food, which their hosts provide for them; hence energy which might otherwise be expended in seeking necessary food, may here be turned to growth and reproduction; thus it is estimated that the fat tapeworm (*Tænia saginata*) increases at the rate of thirteen segments per day, growing 3 cm. per day for the first month and averaging 14 cm. per day for the second month, and producing 150,000,000 eggs per year.

2. Subject to natural selection, for the life-cycles are often very complex, hence in such cases the chances that any one egg has of reaching sexual maturity are very small, so that individuals which are only slightly fertile would probably not be represented by many generations.

3. In accordance with the *general biological law* (not without exceptions) that the smaller an animal, the more fertile it is; we should therefore naturally expect a pinworm to be more fertile than a cow.

Resistance of Parasites.—Some parasites, especially in their egg and encysted stages, are exceedingly resistant to external influences: the Persian argas may live five years without food; *Cysticercus cellulosæ* may live four weeks or so after its host is dead; trichinæ may live for months after their host (hog) is slaughtered; eggs with thick shells (eelworms, whipworms, *Tænia*) are more resistant than eggs with thin shells (hookworms, pinworms, dwarf tapeworm).

Seasonal Periodicity.—Some parasites show a decided seasonal periodicity: hookworms have a better chance to develop in warm, moist months than in cold or hot dry seasons; and in general this obtains for worms

which do not require an intermediate host. For certain worms (as trematodes) which do require an intermediate host (as snails) the seasonal periodicity depends upon the seasonal activity of this host, and this activity may depend upon various factors, such as moisture and warmth.

Origin of Parasites.—Parasites, like other animals, have two origins: namely:

1. The *ontogenetic* origin, or origin of the individual. Contrary to ideas held some decades ago, it is now known that there is no such phenomenon as a spontaneous generation of parasites, but it is known, on the contrary, that every animal parasite proceeds from some former generation of parasites and that it came into being either through sexual or non-sexual reproduction.

2. The *phylogenetic* origin, or origin of the species. To assume that all parasites were created in the beginning as they exist to-day, would be to stamp Adam as a most remarkable helminthological museum, suffering from many parasitic diseases, of which any one of several could have been fatal. The zoölogist holds that parasites have gradually evolved from free-living animals, that numerous connecting links between the two exist and that this process of evolution is still going on.

Heredity of Parasites.—From the strict embryological point of view, it would be impossible to fulfil the condition necessary to demonstrate the heredity of any infectious disease in man, and when we speak of the heredity of these maladies in the higher animals it should be recalled that we are using the term “heredity” rather loosely. No parasitic disease is known to be hereditary in man, though we know of several diseases in lower animals (as in insects and ticks) which are hereditary in a stricter sense of the term; namely, the sexual products are infected before fertilization occurs.

Influence of Parasites upon their Hosts.—Views regarding the injurious effects of parasites have passed from extreme to extreme, some authors going so far as to attribute to some parasites injurious actions which they surely do not have, and others going so far in the opposite direction as to see in the parasites a supposed advantage or even a necessity to the host. Let us recall, however, that the injury done may vary with the species, size, location, and number of the parasites, and with the condition and age of the host. This injury may be accomplished in various ways:

- (1) Nourishment is taken which should go to the host, (2) blood is taken by the parasite as food; (3) mechanical pressure irritates or causes atrophy of organs or parts of organs; (4) natural channels may be obstructed; (5) the wandering of the parasite may cause irritation; (6) substances may be excreted which have a toxic influence, and which may change the natural condition of body fluids (blood); (7) injury to the intestinal mucosa or to the skin may form points of entrance for bacterial and protozoan infections.

Such injury does not, as a rule, go on increasing indefinitely in any geometrical progression because of succeeding generations of parasites, for the general rule obtains (with a few exceptions, as in infections with certain protozoa and with the vinegar eel) that *for every adult animal parasite found in the human body a separate embryo or larva must enter*. Thus, hookworms do not multiply generation after generation in the intestine,

but the eggs must leave the patient and the resulting larvæ reënter the body in order to become adult.

Generic and Specific Infections.—In the following discussion, reference will be repeatedly made to infections as being identical or distinct generically or specifically. These terms are used in their zoölogical sense, to express more accurately the relation which the diseases of man bear to those of animals. Thus, it has been reported that *Tania solium* occurs in both man and dog. If this statement were correct, the dog would be a very important factor, from a public health point of view, in spreading *Tania solium* and cysticercosis. The reported presence of this parasite in dogs is however based upon an error of identification, for there is a tapeworm belonging to the genus *Tania* which does occur in dogs but which belongs to a species (*Tania hydatigena*) specifically distinct from, but quite closely (generically) related to, *Tania solium*. Hence, man and dogs, in this instance, have infections which are *generically* identical, since both parasites belong to the same genus, but *specifically* distinct, since the two worms represent distinct species (*T. solium* and *T. hydatigena*). On the other hand there is a specifically identical tapeworm-infection (*Dipylidium caninum*) which is common to dogs and cats and which may occur in man.

Diagnosis of Parasitic Diseases.—The general rule may be laid down that the best method of diagnosing most parasitic diseases is by a microscopic examination: examine *sputum* for suspected parasitic diseases of the lungs; *fæces* for suspected parasitic infections of the intestine and liver; *urine* for suspected parasites of the kidney or bladder; *blood*, *fæces*, and *urine*, for suspected parasitic diseases of the circulatory system; *blood* and *muscle* for suspected infections of the muscle; *blood* for suspected infections of the lymphatic system. In some cases a diagnosis may be made by a gross examination of the fæces. In some parasitic diseases, diagnosis may be safely made upon symptoms, especially if the patient is within the infected area of a given malady. It will be necessary to discuss further the question of diagnosis in connection with the different infections, but the technique of fæcal examinations can best be given here

In *gross* examinations of the stools (for pinworms or expelled hookworms, etc.), the fæces should be shaken up well with warm water and allowed to settle; pour off any floating material and wash the stool in this manner several times; the worms will thus be concentrated.

For *microscopic* examination of fæces, take a small portion of fæcal matter on the end of a match or toothpick, using a separate one for each stool; smear this in a drop of water on a slide; the large 2×3 slide is more convenient than the ordinary 1×3; cover with an ordinary coverglass, avoiding unnecessary pressure, and examine ten such preparations.

For eggs with thick shells (whipworms, large tapeworms, flukes), use a strong illumination; for worms with thin shells (hookworms, pinworms, etc.), use a more moderate illumination; examine first with medium magnification (8 mm. or $\frac{1}{8}$ -inch focal length), later with higher power.

To make permanent mounts of eggs, preserve the material in alcohol; then transfer to 95 parts alcohol plus 5 parts of glycerine; allow the alcohol to evaporate slowly, and when evaporated to glycerine, mount the material in glycerine-jelly.

Treatment.—The *general* rule may be laid down that for verminous infections of the brain, bones, muscles, eye, lungs, liver, kidneys, spleen, blood and lymphatics, there is no satisfactory specific medicinal treatment, although some of these cases may be treated surgically. Intestinal, bladder, and some skin infections by parasites may be treated medicinally. For further details, see under the different parasites.

Prevention.—So far as most verminous parasites in temperate climates are concerned, ordinary habits of cleanliness—such as are found in the educated American, English, and French families; ordinary care in preparing food—as followed by good housekeepers; ordinary methods of meat inspection—as carried on by the federal government; a proper disposal of alvine discharges—as in sewers, or properly constructed privies; and a recognition of the fact that the dog is not a human being, are in themselves sufficient to prevent serious trouble (in form of epidemics) from most parasites in Australia, Canada, England, and the United States. In warm countries protection against mosquitoes will reduce certain verminous affections (filariasis).

Personal Rules of Hygiene.—(1) The use of spring, boiled or filtered water will decrease certain protozoan, fluke and roundworm infections; (2) proper care of meat (protection from flies) and thorough cooking will protect against certain dipterous larvæ, certain tapeworms and trichinosis; (3) avoidance of depraved tastes for insects will aid in protecting against certain tapeworms; (4) keeping the hands and nails clean, especially after handling dogs, will aid in protecting against a certain tapeworm and hydatid disease; (5) personal cleanliness after defecation will aid in protecting against auto-infection with pinworms and *Cysticercus cellulosæ*; (6) wearing shoes in infected areas will help to protect against hookworm infection and the burrowing flea.

Public Rules of Hygiene.—(1) If sewage is used for fertilizing, it is best to grow upon the land so fertilized, only such vegetables as are subjected to cooking before eating; (2) properly dispose of all fæces, especially in schools, asylums, hospitals; (3) interdict nuisances, especially in warmer climates, and upon plantations, in mines and in digging tunnels and canals; (4) meat inspection in the local slaughter houses (the federal inspection covers only the abattoirs engaging in interstate trade); (5) segregate local slaughter houses and place them under the supervision of a competent veterinarian, who might well be a member of the local board of health; (6) keep swine in a less swine-like manner,—especially see that the privy is not near the pig-pen; (7) swine-offal and swill should be first cooked in case they are fed to hogs; (8) destroy all ownerless dogs and keep dogs away from slaughter houses—the dog pound is an institution of practical hygienic importance.

CLASSIFICATION OF ANIMAL PARASITES.

Contrary to early ideas, the parasites do not represent a group of animals closely related to each other systematically, but rather several diverse groups, more or less widely separated but with somewhat similar biological habits. For the details of classification the reader is referred to works on systematic zoölogy; for the purpose of this article, we may divide the animal parasites as follows:

1. Unicellular animals, as the parasites of malaria.....Protozoa.
Pluricellular animals; metazoa..... 2
2. Body more or less flattened dorsoventrally..... 4
Body ordinarily round in transverse section..... 3
3. Body never annulated; never provided with legs; no jaws present... 5
Body annulated, or at least provided with mouth parts; usually breathe through a tracheal system; adults with jointed legs..... 7
4. Intestine, but no anus, present; one or two suckers present; body not segmented; parasitic in liver, lungs, blood, intestine, occasionally elsewhere; flukes..... *Trematoda*, p. 535
Intestine absent; two or four suckers on head; body of adults segmented; adults (tapeworms) parasitic in intestine; larvæ (bladder worms) parasitic elsewhere..... *Cestoda*, p. 557
Intestine and anus present; ventral sucker on posterior end; body annulated like an earthworm; parasitic in upper air-passages, or externally; leeches, bloodsuckers..... *Hirudineæ*, p. 626
5. Intestine absent; armed rostellum present; very rare in man, in intestine; thorn-headed worms..... *Acanthocephali*, p. 604
Intestine present; no armed rostellum..... 6
6. Intestine rudimentary in adult; rare, accidental parasites in intestine of man; hair snakes or horse-hair worms..... *Gordiaceæ*, p. 604
Intestine present; parasitic in intestine, muscles, lymphatics, etc.; very common and important; roundworms..... *Nematoda*, p. 582
7. Six legs present in adult; wings present in most species; larva annulated much like an earthworm; breathe through trachea; adults ectoparasites; occasionally larva is parasitic under skin, or in wounds, or an accidental parasite in the intestine; insects..... *Insecta*, p. 632
Eight legs present in adult, six legs in larva; head and abdomen coalesced; ectoparasites; some burrow under the skin or live in the hair follicles; acarines..... *Acarina*, p. 626
Four claws around the mouth; larva encysted in various organs; adult occasionally parasitic in nasal passages; tongueworms..... *Linguatulidæ*, p. 632
Numerous legs present; occasionally accidental parasites in nasal passage or intestine; thousand-leggers..... *Myriapoda*, p. 632

Organ distribution of parasites, according to their more common habitat.

MORE OR LESS GENERAL.—*Trematoda*: *Paragonimus*, p. 536; *Schistosoma* eggs, p. 550. *Cestode* larvæ: *Tania solium*, p. 574; *Echinococcus*, p. 576; *Sparganum*, p. 581. *Arachnida*: *Linguatula*, p. 632; *Porocephalus*, p. 632.

INTESTINAL TRACT.—*Trematoda*: *Fasciolopsis*, p. 549; *Heterophyes*, p. 549; *Gastrodiscus*, p. 549; *Cladorchis*, p. 549. Adult cestoda: *Tania*, p. 558; *Hymenolepis*, p. 564; *Davainea*, p. 566; *Dipylidium*, p. 567; *Dibothriocephalus*, p. 567; *Diplogonoporus*, p. 569. *Nematoda*: *Ascaris*, p. 596; *Oxyuris*, p. 599; *Trichostrongylus*, p. 602; *Agchylostoma*, p. 584; *Necator*, p. 583; *Uncinaria*, p. 583; *Physaloptera*, p. 602; *Strongyloides*, p. 595; *Trichuris*, p. 602; *Trichinella*, p. 605. *Gordiaceæ*, p. 604. *Acanthocephali*: *Gigantorhynchus*, p. 604. *Insecta*, p. 632.

LIVER.—*Trematoda*: *Fasciola*, p. 543; *Opisthorchis*, p. 540; *Dicrocoelium*, p. 545. *Cestoda*: *Echinococcus*, p. 576.

LUNGS.—*Trematoda*: *Paragonimus*, p. 536. *Nematoda*: *Metastrongylus*, p. 610.

URO-GENITAL SYSTEM.—*Nematoda*: *Anguillula*, p. 624; *Leptodera*, p. 624; *Diectophyme*, p. 624.

LYMPHATIC SYSTEM.—*Nematoda*: *Filaria*, p. 613.

BLOOD.—*Trematoda*: *Schistosoma*, p. 550. *Nematoda*: *Filaria*, larvæ, p. 613.

MUSCLES.—*Nematoda*: *Trichinella*, p. 605.

SUBCUTANEOUS.—*Nematoda*: *Dracunculus*, p. 611; *Filaria*, p. 613; *Agamofilaria*, p. 623; *Rhabditis*, p. 611; *Gnathostoma*, p. 611. *Insecta*, p. 632.

ECTOPARASITES.—*Acarina*, p. 626. *Insecta*, p. 632.

NOMENCLATURE AND TERMINOLOGY.

To the biologist, *nomenclature* deals with the *names* used to designate systematic units, such as families (*Tæniidæ*), genera (*Tænia*), species (*Tænia saginata*), etc. As systematic zoölogists are obliged to use thousands upon thousands of such names, it is advisable that these should be removed, so far as possible, from the influence of individual or national tastes and prejudices; and, in order to make them international in character, Latin has been adopted as the basis for all *technical* names (as opposed to *vernacular* names). The acceptance or rejection of names and the method of writing them are governed by "codes of nomenclature," which may in a certain sense be compared with the medical "code of ethics." For the zoölogists, the International Congress has adopted an "International Code,"¹ (1905) prepared by a permanent international commission of fifteen members. This code is based primarily upon the rules proposed by Linnæus, in 1751, modified to meet the advances in science. In order that no revolutionary principle may be suddenly introduced, the rules of the Congress provide that no proposition for changing the code can be adopted unless submitted to the Commission at least one year prior to the tri-annual meeting of the Congress. The chief points in the code are: (1) The "law of priority," which provides that the valid name for any genus or species is its oldest available name; *i. e.*, available under the code; thus, *Ascaris*, 1758, is an older name than *Fusaria*, 1800, for the eelworm. (2) The "rule of homonyms," which provides (*a*) that when two generically distinct animals have received the same generic name, this name is available only for the earlier genus (thus, when *Trichina* was proposed for a genus of worms by Owen in 1835, it was already in use for a genus of insects, 1832, hence the name cannot be adopted for the worm); and (*b*) that when two species in any given genus have received the same specific name, it is available only in its earlier use (thus, *Tænia murina*, 1845—*Hymenolepis nana*, 1852,—is antedated by *Tænia murina* Gmelin, 1790—*Cysticercus fasciolaris*—hence *murina*, 1845, is not available as name for the dwarf tapeworm, and *nana*, 1852, its oldest synonym, becomes valid). (3) No name can be changed because of its inappropriateness or for any subjective reason, as *names are not definitions*, hence the introduction of *Amaba dysenteriae* for *Amaba coli* was not permissible under the code.

Physicians are urged to acquaint themselves with the code, before they publish or change zoölogical names, as it is often difficult to understand whether or not a physician is using a new name in a zoölogical sense, and further because names are too frequently proposed contrary to zoölogical customs.

The question is frequently asked, why zoölogists do not adopt, for the parasites, the names already known to physicians. The answer is simple: (1) The animals known in medicine form an almost insignificant fraction of one per mille of the animals with which we have to deal, and it would be a very dangerous precedent to make exceptions for this group;

¹See Stiles, 1905, pp 1-50, the "International Code of Zoölogical Nomenclature as applied to Medicine." *Bulletin 24, Hygienic Laboratory U. S. Public Health and Marine Hospital Service, Washington*

(2) when physicians discover that two diseases have been confused under one name, or one disease has been given two or ten names, they do not hesitate to straighten out the terminology, yet the terms used by physicians go only into the thousands, while the names in zoölogy run into the millions, hence zoölogists must be even more rigid than physicians in respect to technical names. Would any physician to-day, for instance, claim that trichinosis should be called typhoid, on the ground that before 1860 the two diseases were confused? (3) Advance in microscopic technique and instruments has made as great changes in zoölogy as it has in medicine, and zoölogists are adapting their nomenclature to the changes in classification rendered necessary by the new discoveries. We do not, to-day, speak of *Tænia lata* and *Bothriocephalus latus* for the simple reason that the species in question is now known to belong neither to *Tænia* nor to *Bothriocephalus*.

Terminology, in distinction to nomenclature, deals with the technical terms of parts, organs, functions, conditions, etc. No recognized code of rules governs the names of the muscles of the body or the names of diseases. A man adopts a technical term because it has been taught to him, or he changes it, if a better name occurs to him, and, finally, men adopt the names best known to them. Thus, terminology is largely subjective and such incongruities occur as using a term like "spotted fever" for two or three different diseases; while in the United States "typhus" refers to one disease, in Germany it is frequently used for another malady (typhoid).

For parasitic diseases, we may distinguish three different kinds of terms in particular: (1) Latin terms based upon the zoölogical generic names (as *distomatosis*, *tæniasis*, *trichinosis*, *acariasis*, etc.); (2) vernacular terms based upon some symptom, geographical locality, etc., (itch, Egyptian hæmaturia); (3) vernacular terms based upon a vernacular name of the parasite (hookworm disease). For international use, Latin terms are by all means preferable, as they do not need to be translated, but for current use vernacular terms are often very convenient.

Bibliography.—In a short article of this kind it is impossible to give a full bibliography, for which the reader is referred to Huber's *Bibliographie der klinischen Helminthologie* (1895, 1898, 1899–1900), or Stiles and Hassall's Index Catalogue of Medical and Veterinary Zoölogy (*Bull.* 39, U. S. Bureau of Animal Industry) and Looss (1905).

For annual reviews of literature on parasites, see especially *Zoölogical Record* and *Archiv für Naturgeschichte*. For current literature, with original articles, reviews, and current bibliographies, see especially, *Archives de Parasitologie*, *Centralblatt für Bakteriologie*, *Parasitenkunde und Infektionskrankheiten*, *Zoologischer Anzeiger*, and *Zoologisches Centralblatt*. The current zoölogical references can be purchased in card form from the Concilium Bibliographicum, Zurich. The most extensive card catalogue on the subject is the combined index in the Zoölogical Divisions of the U. S. Public Health and Marine Hospital Service and the U. S. Bureau of Animal Industry.

Determination of Specimens.—Specimens of animal parasites of man are determined for physicians, free of charge, by the Division of Zoölogy, Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, Washington, D. C. Such material should be forwarded in alcohol (about 50 to 70 per cent.).

Government Publications.—For U.S. government publications on animal parasites, application should be made to the "Keeper of Public Documents, Washington, D. C.," or (either directly or through a Senator or Congressman) to the Chief of the Bureau by which the document was issued.

CHAPTER XXIV.

DISTOMATOSIS-TREMATODE OR FLUKE INFECTIONS.¹

By CHARLES WARDELL STILES, PH. D., D. Sc.

Terminology.—The general term *distomatosis* or *distomiasis* is based upon *Distoma* which has been used by many authors as the collective genus for the trematodes, more especially for the so-called digenetic forms. As a generic name for these parasites *Distoma* is not valid and the species which have been included in this genus are now distributed over a large number of well defined genera. Upon the names of these more restricted genera, Latin terms have been based to designate infections with species of the respective genera (as *fascioliasis*, *opisthorchiasis*, *paragonimiasis*). The word “distomatosis” has been combined with the name of the organ affected (as pulmonary distomatosis); while for some of the diseases, there are well-known vernacular terms (liver-fluke disease, liver rot, etc.).

Different Kinds of Trematode Diseases in Man.—In man there are four different clinical classes of trematode diseases which may be regarded as typical, in the sense that in these four instances the infection of man by certain trematodes is more or less normal in the life-cycle of the parasite under consideration. These cases are:

1. A pulmonary distomatosis, with cerebral or other infection as secondary;
2. An hepatic distomatosis, with splenic or intestinal infection as secondary;
3. An intestinal distomatosis; and
4. A venal distomatosis. In addition we find recorded rare instances of
5. An ophthalmic distomatosis, which may be an accidental secondary form of hepatic distomatosis.

All of the parasites in question, with the exception of the blood-flukes, are hermaphrodites, and possess an oral or an oral and a ventral sucker, a mouth, and two blind intestinal cæca. The life-cycle is quite complicated and may involve two or more generations which live outside of man. The parasites may require an intermediate host or in some cases indications are not lacking that direct infection may perhaps occur.

¹For more detailed zoölogical descriptions, in English, of these parasites, see Stiles, 1904, pp. 1–66, figs. 1–48; “Illustrated Key to the Trematode Parasites of Man.” *Bulletin 17, Hygienic Laboratory, U. S. Public Health and Marine Hospital Service*, Washington. For the most recent general discussion of trematodes, in English, see Ward, 1903, pp. 860–873; for keys (in English) to the numerous new genera of trematodes, see Pratt, 1900 and 1902.

PULMONARY DISTOMATOSIS.—LUNG-FLUKE DISEASE.

Paragonimiasis or Parasitic Hæmoptysis.¹—**Geographical Distribution.**—The Asiatic region, particularly Japan and China, appears to be the special home of this disease in man, although a generically related if not specifically identical infection occurs also as an endemic disease in hogs in the United States. It is reported also for the Philippines, Formosa and Korea and occasionally imported cases are found in various other places.

Zoölogical Distribution.—It is difficult at present to determine the original host of this disease but it is known to occur more or less frequently in man, cats, tigers, dogs, swine; and Looss (1905) says it occurs in cattle. Generically identical but supposedly specifically distinct infections occur in the Brazilian otter and the Indian ichneumon. Pulmonary distomatosis is occasionally found in cattle as an accidental manifestation of fascioliasis, and lung infection with other genera of flukes is exceedingly common in snakes, toads, and frogs.

The Parasite.—*Paragonimus westermani*² (Kerbert, 1878) is a plump, depressed, oval, or pyriform, pinkish to reddish-brown (live specimens), spinose fluke 7.5 to 16 mm. long by 4 to 8 mm. broad by 2 to 5 mm. thick; with branched testicles and ovary but unbranched intestinal cæca; eggs yellow, 77 to 102.5 by 40 to 75 μ with distinct operculum but containing no miracidium when discharged. The adult parasites are found in cysts, one to three together, in the lungs, especially in upper lobes, occasionally in the pleura, liver, abdominal cavity, brain, orbit, lower eyelid, cervical glands, scrotum and various other parts of the body.

Source of Infection.—Unknown. The eggs develop a ciliated miracidium (embryo) in water in four to eight weeks; this probably enters some snail. The infecting stage probably enters man with contaminated food or water; Katsurada thinks it may pass directly from the mouth to the bronchi, or if swallowed, from the stomach up the œsophagus and down into the lungs, or perhaps from the stomach through the stomach wall to the mesenterium and from there by the lymphatics to the final point of rest.

Frequency.—More frequent in mountainous localities (Katsurada); chiefly in peasants, more common in males than in females (88.57 per cent. to 11.43 per cent. in 481 collated cases) and between the ages of sixteen and thirty years; in some localities 20 to 73 per cent. of the lung-fluke patients give a history of other cases in the same family (Katsurada), while in other places the family history is reported as negative. It is stated that in certain parts of Formosa, 15 per cent. of the inhabitants are affected; in one Japanese village nearly all the inhabitants

¹For a more detailed discussion in English, with bibliography, see Stiles and Hassall, 1900, pp. 560-611.

²SYNONYMS.—*Distoma westermani* Kerbert, 1878; *Distoma ringeri* Cobbold, 1880; *Distoma pulmonis* Kiyona, Suga, and Yamagata, 1881; *Distoma pulmonale* Bætz, 1883; *Distoma pulmonum* (Bætz) Tomono Hidekata, 1883; *Distoma cerebrale* Yamagiwa, 1890.

In the lists of synonyms given in this paper, only the more common or the newer names are mentioned; for full lists of synonyms the reader is referred to the special literature on the various species.

harbor the parasite (Bælz). In a hospital in Okayama, 0.4 per cent. of the 20,793 patients from 1891 to 1897 showed infection (Inouye). Various Japanese physicians report that from 2 to 14 per cent. of their patients suffering from respiratory troubles harbor this fluke. Inouye (1903) has collected 19 cases of brain infection. Frequency doubtless varies with occupation leading to exposure to infection. In Okayama, 7 of 130 dogs examined showed infection. From 2 to 28, perhaps more, parasites occur in each patient.

Duration.—The longevity of the individual parasite is not established but cases are reported with histories extending over ten, twenty and even thirty years, these prolonged cases probably being due to repeated infections.

Symptoms.—The symptoms vary according to the location and number of the parasites present.

(a) *Lung Infection, Parasitic Hæmoptysis.*—This is the usual and uncomplicated (primary) form of the disease and represents the typical paragonimiasis or pulmonary distomatosis as found in man. The onset may be so gradual that the beginning can not be recognized with certainty. The only constant and specific characteristic is the presence of the eggs in the sputum; it is estimated that as many as 12,000 ova may be expectorated daily. The *sputum* is yellow to red or rusty brown, due to the presence of the microscopic eggs, and has a peculiar odor, partially due to blood; poor in water and rich in mucus, it varies from a small amount to 100 Cc. daily; blood is common but not constant, being present in points, strings, or larger amounts; while severe hemorrhages are not common, Bælz reports a case with a loss of a pound of blood within a few hours; the amount of blood, which is always arterial (Taylor), increases after violent exertion, irregularities in diet, use of alcohol, brain strain, excess in venery, tobacco smoking and in cold weather; intense anæmia may result; the sputum is often discharged in spirals, resembling Curschmann's asthma spirals, and contains eggs, blood, pus, mucus threads, alveolar and bronchial cells, numerous Charcot's crystals; Taylor and Mimachi have each observed an expelled worm. There may be hoarseness or a chronic cough, usually light, rarely so severe as to disturb sleep and most urgent in the morning upon rising.

As the disease progresses the periods of cough and hæmoptysis become more frequent and prolonged, tending more or less toward permanency and the amount of expectoration increases from a slight quantity at the onset to a much greater quantity later—as much as 10 to 12 ounces in a few hours. All symptoms increase after physical exertion. Physical examination does not usually reveal anything abnormal except in severe cases; Inouye (1903) reports retraction thoracis as among the most common changes noticed, with contraction of the infrascapular portion; as the patient fails, auscultation shows diminished respiratory murmur, the breath sounds being vesicular but rarely weak, occasionally bronchial in character with dry or moist rales. Scheube observed repeatedly that one side, probably the infected, expands less than the other. Inouye reports unilateral or bilateral signs appreciable on percussion in 86 per cent. of 92 patients examined; only 1 of these had tuberculosis. The temperature is normal or but slightly elevated even in severe cases. The patient may become exhausted by cough and hemorrhage; he also

becomes deeply anæmic, and suffers from dyspnoea on slight exertion. Slight œdema often occurs. There is a sensation in the chest variously described as of oppression or of heat or of mere irritation. Occasionally there are wandering pains in the chest, "most probably neuralgic." Inouye reports chest pains in 37 per cent. of 92 cases examined; in 28 of these (82 per cent.) retraction thoracis was present; the pains were due to fresh or old pleurisy. After rest in bed all symptoms may abate except the cough and expectoration and months may pass before a relapse occurs. Gradually the constitution becomes undermined, convalescence becomes less complete, periods of rest become shorter, those of prostration longer and more severe, œdema and anæmia increase and at last the exhausted patient dies.

The *lethality* of the uncomplicated form of the disease does not seem to be established but it doubtless varies with the intensity of the infection.

(b) *Brain Infection*.—If the worms or their eggs gain access to the brain, a *cerebral distomatosis* develops, resulting in epileptiform attacks (Jacksonian or cortical epilepsy). It does not appear to be established in what percentage of cases this complication appears but it is an extremely serious and fatal form; Inouye (1903) reports that of 92 patients with paragonimiasis, 3 showed brain symptoms (headache, dizziness, weak memory), 2 epilepsy, and 1 epilepsy and left hemiplegia; he has collected, in all, 19 cases; of these, 8 showed general spasms, 4 dextral, 2 sinistral spasms, 5 had hemiplegia, 5 spasm with weakness of the same side, other symptoms (paresis of right arm, color ring, etc.) being less frequent. The epileptic attacks may at first be a month or so apart but they gradually increase in frequency and severity until death.

(c) *Infection in Eyelid*.—Several cases have been reported in which the parasite lodged in the eyelid, forming a tumor which resulted in obstruction to the sight and to movement of the eye.

(d) *Liver Infection*.—A purely accidental hepatic distomatosis may occur in connection with pulmonary distomatosis, in that eggs of the lung-fluke may be found in the liver. Such occurrence, however, can hardly result in a typical hepatic distomatosis and it is possibly an open question whether some of these cases were not due to the newly recognized Japanese blood-fluke (see p. 550).

(e) *Infection of Other Organs*.—Cysts of lung-fluke eggs may also occur in the mesentery, omentum, etc., but thus far such lesions do not appear to have produced any serious symptoms.

Pathology.—(a) *Lung Infection*.—Occasionally deep, more commonly superficially in the lung, or directly under the pleura, are found roundish or flat cysts about as large as the end of the little finger, and containing from one to three parasites or in some cases only caseous contents. Katsurada (1900) is of the opinion that these cysts represent dilated bronchi, although he does not deny that cavities in the lung tissue may form independently of the bronchi; the lumen communicates with the neighboring bronchi by one large or numerous small openings and the different cysts may communicate with each other by means of direct or long irregular tubes; the septa between the tunnels may break down and a considerable cavity be thus formed (Manson); the wall of the cyst is rather stout, grayish-white, about 1 mm. thick; the inner surface is usually smooth, and the lumen may contain a reddish or brownish-green slimy fluid.

Katsurada (1900) states that at first the changes are a more or less intense bronchitis and peribronchitis of a catarrhal, hemorrhagic or more purulent character. When the worms settle in the bronchi, the walls undergo an inflammatory infiltration, a richly vascularized granulation with connective tissue forms, and the original structure of the bronchi becomes lost. The bronchitis is caused not only by the worms but also by their eggs. An adhesive pleuritis may develop.

(b) *Brain Infection*.—Yamagiwa reports disseminated circumscribed foci of trematode eggs, usually also with giant cells, in the cortical substance of the occipital, parietal and central lobes of the brain; surrounded by connective tissue and round-cell infiltration; thickening of the wall of the bloodvessels, especially of the adventitia, and obliteration of some of the branches; associated with lesions in the lungs containing eggs of the same parasite and giant cells.

(c) *Liver Infection*.—Yamagiwa reports cirrhosis of the liver resulting from emboli of eggs in the portal area (or perhaps co-existence of these fluke-egg emboli with cirrhosis due to other causes). See also p. 538.

(d) *Infection of Other Organs*.—Cysts containing these fluke-eggs, and fibrous nodules have been found in the mediastinum, diaphragm, mesenterium, and walls of the intestine; Otani is said to have found abscesses in the cervical and inguinal regions caused by trematodes. Eggs have been noticed in the contents of the intestine but these may have resulted from swallowed sputa.

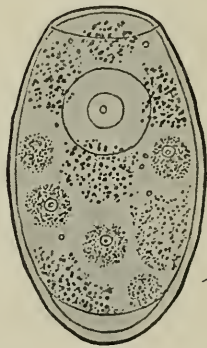
Clinical Diagnosis.—This disease was long confused with tuberculosis from which it may be readily distinguished by microscopic examination of the unstained sputum to find the characteristic egg.

Treatment.—No specific treatment is known. Inhalations have proved unsatisfactory. By sending the patient to an uninfected locality further infection is avoided and with the lapse of time (the length of which is not known) the parasites may finally die and become disintegrated or may be coughed up. Surgical interference has been suggested for cases in which the parasite can be definitely located.

Prevention.—(1) Destruction of infected sputum; destruction of cats and dogs showing the same disease; destruction of the lungs of swine showing the same infection. (2) Use of filtered or boiled drinking-water; thorough washing of vegetables; thorough cooking of snails when these are used for food. These latter precautions are based upon analogy, as nothing positive can be stated in this line until the life-history of the parasite is known.

Pulmonary Distomatosis Due to *Fasciola Gigantica*.—One case of pulmonary distomatosis in man has been reported as due to *Fasciola gigantica*. This was doubtless a case of chance parasitism, as man is not known to be a normal host for *Fasciola* and as the liver, not the lungs, is the normal organ in which *Fasciola* occurs. The parasite in question is common in Africa in the liver of buffalo, cattle, sheep and goats; it was

FIG. 35.



Egg of lung-fluke showing ovicell, yolk cells and operculum. $\times 100$. (Katsurada.)

originally described for the giraffe; it is similar to *F. hepatica* in structure, but much narrower, measuring 25 to 75 mm. long by 3 to 12 mm. broad; eggs 145 to 190 by 75 to 90 μ .

HEPATIC DISTOMATOSIS.—LIVER-FLUKE DISEASE.

At least six different species of liver-flukes, representing three different genera (*Opisthorchis*, *Dicrocoelium* and *Fasciola*), have been found in connection with hepatic distomatosis. Infections with *Opisthorchis* are common to man, dogs and cats, and are much more frequent in man than are infections with *Dicrocoelium* and *Fasciola*, which man has in common with certain food animals, particularly cattle and sheep. Of the six specific infections in question, one (an Asiatic disease) is much more important than all the rest combined.

Source of Infection.—For only two of these infections, namely for the fascioliasis, due to *Fasciola hepatica*, and opisthorchiasis, due to *Opisthorchis felineus*, is the source of infection known (see pp. 541, 546); for all of the others, this is a matter of speculation based upon analogy and circumstantial evidence.

Clinical Diagnosis.—This is identical for all six infections. Make a microscopic examination of the unstained faeces for eggs; also of the sputum and urine, as the ova in pulmonary and venal distomatosis may be discharged per anum; hence, finding eggs in the faeces, without excluding pulmonary and venal distomatosis, may lead to error.

Treatment.—There is no specific treatment known for any form of hepatic distomatosis; remove the patient to a non-infected area or, if he be kept at home, avoid further infection and give good nourishing food.

Prevention.—The same general principles apply to all six infections.

Opisthorchiasis.

The term opisthorchiasis has been introduced by Looss (1905) to designate infection with flukes belonging to the genus *Opisthorchis*, a group characterized chiefly by the position of the testicles near the posterior extremity of the body. In man we may distinguish at present three distinct infections by species of this genus; in order of importance these are the Asiatic, the European and the Indian species.

Asiatic Opisthorchiasis or Japanese Liver-Fluke Disease—Geographical Distribution.—This infection is endemic in Asia, more especially in Japan and China, but it is also found in the Philippines, India, Formosa, Mauritius, Annam, Tonkin and Korea, and imported cases are occasionally reported for other parts of the world. About twenty imported cases have been recorded in the United States.

Zoological Distribution.—So far as can be judged at present, man must be considered one of the normal hosts of this parasite, but cats and dogs also appear to be normal hosts. Generically identical but specifically distinct infections are found in quite a number of other animals.

The Parasite.—The Asiatic liver-fluke disease is caused by *Opisthorchis sinensis*,¹ an elongate, lanceolate, non-spinose trematode, 9.7 to 20 mm. long by 2 to 5 mm. broad. Its chief anatomical characteristic is the branched condition of the testicles. Eggs, 24 to 30 by 15 to 17.5 μ , exceptionally 35 by 19, 20 by 15.7, or 22.5 by 15 μ ; the eggs are somewhat thicker than those of *O. felineus*, dark brown, with sharply defined operculum, occasionally with small knob at posterior end and containing a ciliated miracidium at oviposition. The adult worm inhabits particularly the gall-ducts but may be found in the gall-bladder and in the pancreatic duct and (probably in the act of wandering) also in the duodenum and stomach. Katsurada (1900) found it in the pancreas in 9 out of 67 infections.

Source of Infection.—The life-history of species of the genus *Opisthorchis* is unknown (except *O. felineus*, contracted from eating raw fish), hence the source of infection can not be definitely stated but the microscopic anatomy of the embryo shows that at least part of its life is spent in water; it probably enters some snail. The probabilities are that infection of man takes place either directly from water by swallowing the free cercaria or indirectly through eating some water-animal (snail or fish) or through food contaminated by infected water.

Frequency.—According to Taylor, some native practitioners in the infected villages estimate that 1 in 7 or 1 in 5 of the entire local population is infected, irrespective of age, sex or physical condition, and where one member of a family is infected several members are likely to harbor the worm. Katsurada (1900) recognized 654 cases of infection in 1,075 persons examined (namely 60.8 per cent.) in three villages engaged chiefly in rice culture and in a region abounding in canals with dirty water. It is also said that in Japan, in certain littoral regions where the water is poor, 20 per cent. of the inhabitants are infected, while in localities a few miles distant and with better water the parasite is comparatively rare. In some patients only a few parasites are present while in others large numbers are found. Thus Katsurada (1900) reports that of 72 cadavers examined, 4 contained from 2,216 to 4,361 worms each, and Blanchard (1901) reports 1 infection with over 10,000 parasites.

Duration.—Cases of infection of two to five years standing seem to be common, but the longevity of the individual parasite does not seem to be determined.

Symptoms.—To a certain extent these depend upon the number of parasites present, so that light infections may escape attention unless a chance microscopic examination is made. Usually there is at first increased, exceptionally decreased, appetite. In heavy infections, one of the first and most pronounced symptoms is the enlargement and tenderness of the liver, preceded, attended, or followed by diarrhœa; the stools become irregular; the diarrhœa is at first irregular and intermittent, the attacks becoming more and more frequent and prolonged, until after two to five years there may be hardly any interval between them; the stools

¹SYNONYMS.—*Distoma sinense* Cobbold, 1875; *Distomum spathulatum* Leuckart, 1876 (not Creplin, 1849; for *spatulatum* Rudolphi, 1819); *Distomum spatulatum* Cobbold, 1879 (not Rudolphi, 1819); *Distoma japonicum* R. Blanchard, 1886 or 1888; *Opisthorchis sinensis* (Cobbold, 1875) R. Blanchard, 1895; *Dicrocoelium sinense* (Cobbold) Moniez, 1896.

may be light, or dark and bloody and may reach twelve per day; in some cases blood is present only at irregular intervals, in others the bloody diarrhoea becomes almost constant. The liver continues to increase in size, in some cases reaching the navel, though at times it apparently diminishes temporarily; there may be tenderness over the hepatic region or more or less dull pain and pressure may result in excruciating agony; jaundice, sometimes intermittent, is a frequent symptom; there is generally a dark ashen discoloration of the skin. The temperature may be normal or may increase to 100° F. After a time anasarca, likewise intermittent, appears and affects the legs especially. Night blindness is likely to occur. Epistaxis is rather common. Ascites often occurs, may increase for a time, then gradually diminish, to appear again and again. The patient is reduced by diarrhoea, becomes emaciated and grows anæmic and weak, but the appetite is usually preserved. It frequently happens that the patient is reduced so low that life is despaired of, yet he may gradually rally and apparently become almost well (Taylor, 1884). Later, however, relapse occurs and the same process is repeated again and again, ground being lost each time, until at length, worn out and exhausted, the patient dies after many years of illness. In some cases enlargement of the spleen is noticed and occasionally a chronic gastrointestinal catarrh is reported. In prolonged cases the liver becomes smaller.

Lethality.—Of 1,495 cases, compiled for the province of Okayama, Katsurada (1900) reports 238 as fatal (16 per cent.).

Pathology.—As the parasites are situated chiefly in the liver, we naturally expect this to be the chief seat of the lesions; in fresh cases it is enlarged, sometimes hyperæmic, in prolonged cases normal or decreased in size and of more or less cirrhotic appearance. The superficial gall-ducts are prominent, white, opaque, and irregularly thickened; worms may be pressed out singly or in bunches in the thick, slimy, yellow to dark brown bile. The lesions are particularly of two kinds, involving the biliary canals and the hepatic parenchyma. When the worms enter the bile canals they obstruct the lumen more or less completely; the first result is a bile stasis with resulting dilatation of the canals; the latter acquire considerable dimensions, while both epithelial and subepithelial layers undergo profound modifications. Opinion has been expressed that these changes are due to mechanical causes; without doubt these are important but the parasites seem to do other damage than acting simply as foreign bodies, for in case of infection with *Fasciola hepatica*, Railliet has shown that the parasites suck blood from the capillaries in the walls of the canals. The lining of the ducts shows catarrhal irritation; the discharged mucus contributes to the occlusion of the canals; the glands undergo considerable hypertrophy which increases progressively and develops an extended adenoma; the newly-formed bile canaliculi are numerous at the side of the chief canal with which they communicate; in sections nodules of several millimeters in thickness may be found which contain sections of a number of canals. The connective-tissue layer of the canals undergoes very active proliferation and may attain an enormous thickness, its outer layer showing more or less small cell infiltration; it pushes before it the epithelium and thus contributes to the obliteration of the canal; it also compresses the hepatic tissue at the expense of which it lodges and which then under-

goes secondary lesions. A cirrhosis develops which, with time, acquires considerable proportions. The hepatic tissue undergoes granular and fatty degenerations and, little by little, atrophies. The lesions have a marked influence on the general nutrition; the arrest of bile causes digestive trouble; compression of the branches of the portal vein causes stasis toward its origin from which ascites results (Blanchard, 1901c); Katsurada (1900) reports ascites in 15 out of 76 cases as a result of the parasitic interstitial hepatitis or of the stasis in the portal vein. Of the 76 cases reported by Katsurada, 2 had gall-stones in the gall-bladder (compare also a similar instance reported by Kirchner for infection with *Dicrocoelium lanceatum*) and 2 showed primary malignant growths in the liver, 1 of which was carcinoma; the parasites had caused a hepatitis in the course of which carcinomatous growth developed from the epithelium of the newly-formed gall-ducts. The gall-bladder may be greatly enlarged. The spleen was enlarged in 6 of the 15 cases in which ascites was present, but in 1 case this organ was considerably reduced in size. In especially severe cases Katsurada frequently found catarrhal changes in the stomach and intestine. Of 76 cases, 9 (11.8 per cent.) either showed or gave a history of icterus; of the 15 cases with ascites, icterus was present in 7 (46.6 per cent.).

Clinical Diagnosis.—Microscopic examination of unstained faeces to find the egg of the parasite is necessary. When in an infected locality a case of enlargement of the liver and bloody diarrhoea is seen, careful examination of the faeces is usually rewarded by finding the eggs.

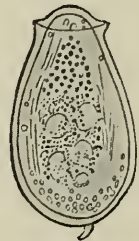
Treatment.—No specific treatment is known. Whether any severe cases ever fully recover is not stated but it seems, *a priori*, that a change of locality to uninfected districts, thus preventing further infection of the patient, should be attended by at least a prolongation of life. Taylor (1884) says that it is doubtful whether recovery takes place after one becomes a victim of this disease, by which he probably does not refer to the light infections. Katsurada (1900) suggests the advisability of laparotomy in some cases, in order to press the parasites out of the gall-ducts into the intestines.

Prevention.—(1) Destruction of all cats and dogs affected with this parasite, and disinfection, by heat or by drying, of all faeces from infected persons. (2) Until the life-history of the parasite is known, the precautions mentioned under Prevention (2), p. 539.

Siberian Opisthorchiasis or Siberian Liver-fluke Disease.—**Geographical Distribution.**—The parasite in question is reported for France, Germany, Holland, Italy and Russia, but cases in man are known only for Prussia (Germany) and Siberia. The reported presence of this parasite in the United States is based upon a misdetermination (*Opisthorchis pseudofelineus*).

Zoological Distribution.—The cat, and possibly the dog, the fox (*Vulpes vulpes*), and the glutton (*Gulo borealis*) form the natural hosts for this infection; it is not yet thoroughly established whether man is a natural or a chance host for the parasite though indications point to the latter condition.

FIG. 36.



Egg of Asiatic liver-fluke greatly enlarged. (Katsurada.)

The Parasite.—This particular infection is caused by the European cat-fluke (*Opisthorchis felinus*), a lanceolate, non-spinose worm, measuring from 8 to 15, rarely to 18 mm. long by 1.25 to 2.5 mm. broad; the testicles are lobate, but not branched; eggs oval, yellow-brown, 26 to 30 by 11 to 15 μ , one side slightly flatter than the other; with sharply defined operculum on the more acute pole and containing a ciliated miracidium at oviposition. The adult parasites inhabit the gall-ducts but are occasionally found in the pancreas and duodenum.

Source of Infection.—The embryo does not hatch in water but it hatches in snails belonging to the genus *Limnaea*, although it does not develop further in this host. From circumstantial evidence suspicion has fallen upon raw fish as a source of infection and Askanazy (1906) has traced the infection to the dace (*Leuciscus rutilus*) and the ide or orf (*Idus idus*).

Frequency.—This is an exceedingly common parasite of cats in some parts of Europe. Winogradoff (1892) reports 8 cases of infection (6.45 per cent.) in man in 124 autopsies at Tomsk, Siberia; Askanazy (1900b) reports 5 cases (all males) from Heydekrug district, Prussia; and Kurimoto (1900) and Kholodovsky are authority for 1 case in St. Petersburg, Russia, in a patient who had been in Siberia. Thus, recent literature shows that this is by no means a rare parasite in man. In the cases reported for man, there were several to a thousand (Askanazy, 1901) parasites present.

Winogradoff has reported an additional case of infection with a small spinose fluke which he supposed was a young *O. felineus*. Braun has, however, pointed out that this might perhaps be a *Metorchis truncatus*, a small spinose fluke which occurs in the dog, cat, fox, glutton, and seal.

Duration.—Unknown. In one case probably nearly three years.

Symptoms.—The cases that have been found have not all been carefully studied from a clinical point of view. In general, approximately the same clinical picture can be expected which is found in corresponding infections with the Asiatic fluke, for the worms are very closely related and the lesions more or less identical. According to Askanazy (1900b), Winogradoff reported icterus in 5 of his cases, decreased liver in 5 cases, enlarged liver in 2 cases, ascites in 3 cases. In Askanazy's third case he reported (1901) icterus and bilirubinuria in a cachectic man with a very large, hard growth in the liver, enlargement of the gall-bladder and colic-like pains.

Lethality.—In none of the cases reported is the parasite given as the direct cause of death.

Pathology.—In general this is similar to that of Asiatic opisthorchiasis, except that no such severe infections have been studied. Askanazy (1900b) summarizes the pathology as cholangitis catarrhalis and pericholangitis fibrosa or as Virchow described it in fascioliasis, as a chronic choleperitonitis and fibrous periportitis. Bossuat (1902) summarizes the condition as an irritation of the walls of the biliary canals, a thickening with pisiform dilatations, followed by a veritable cirrhosis. In two of the cases studied by Askanazy, he reports (1901) carcinoma (*cf.* above, p. 543) of the liver which he believes was indirectly caused by the parasites. The free eggs in the ducts were surrounded by eosinophile pus cells (Askan-

azy, 1900b). The pancreatic duct showed the same changes as the gall-ducts. Charcot's crystals were present in the fæces.

Clinical Diagnosis and Treatment.—See p. 543.

Prevention.—See p. 543. In view of the fact that fishes form the intermediate host, it will be well to avoid eating raw fish. This avoidance also recommends itself on general principles in connection with the prevention of infection with the broad Russian tapeworm.

Indian Opisthorchiasis or Indian Liver-Fluke Disease—Geographical Distribution.—Thus far reported only for Calcutta, India, unless Winogradoff's ninth case (which Braun thinks may perhaps have been due to *Metorchis truncatus*) belongs here (?). Ijima reports a spinose fluke for cats in Japan which might perhaps be identical with this species.¹

Zoölogical Distribution.—Man and dogs. It is not yet known whether these are the normal or merely chance hosts for this infection. The view that this parasite occurs in the North American red fox (*Canis fulvus*) is based upon an error of identification.

The Parasite.—The Indian liver-fluke, *Opisthorchis noverca* Braun, 1903, is a lanceolate, spinose fluke, 9 to 12.5 mm. long by 2.5 mm. broad, which lives in the gall-ducts. Eggs oval, 34 by 19 to 21 μ .

Symptoms.—In general, these are probably the same as for other species of this genus, see p. 541.

Source of Infection, Duration, Lethality, and Prevention.—Unknown.

Frequency.—Only two cases (McConnell, 1876 and 1878) known.

LANCET FLUKE INFECTION.

Geographical Distribution.—This infection seems to be primarily one of Continental Europe. Its exact distribution can not be stated, as there has been considerable confusion in the determinations of infections with this and other lanceolate parasites. Aside from Europe, it is reported also for Northern Africa, Siberia, Turkestan, and North and South America. American specimens have never been seen by the writer.

Zoölogical Distribution.—The same confusion noticed in connection with the geographical distribution also exists in reference to the hosts. Apparently cattle and sheep are the normal hosts for this disease, which is also reported for the goat, deer (Hirsch), horse, ass, hog, hare, rabbit, and man. Certainly many and possibly all of the reported occurrences of this infection in carnivorous animals (dogs and cats) are based upon errors of identification, as pointed out by Braun (1893c and f).

The Parasite.—The lancet fluke (*Dicrocoelium lanceatum* Stiles and Hassall, 1896) is a non-spinose, lanceolate trematode, 4 to 9 mm. long by 2 to 2.4 mm broad, characterized by the anterior position of the testicles, which are between the acetabulum and the ovary, and by the posterior position of the uterus. Eggs, dark brown, thick-shelled, 38 to 45 by 20 to 30 μ , with a distinct operculum and containing a ciliated miracidium when oviposited; the embryo is provided with two dark spots in posterior portion.

¹Looss, 1905, p. 91.

Source of Infection.—Unknown. Embryos hatch in the intestine of slugs (*Arionidae*) but not in water; they do not, however, develop further in these mollusks.

Frequency.—While the parasite is quite common in cattle and sheep, only 7 cases of its occurrence in man have been reported. It is doubtless purely an accidental parasite for man.

Duration.—Unknown.

Symptoms, Lethality, and Pathology.—Probably not serious, as only light infections are likely to occur in man. Kirchner reports 1 case with gall-stones. It seems not impossible that Mehlis's case, in which a woman vomited 50 specimens of this parasite and 9 of *Fasciola hepatica*, resulted from eating infected liver which was not thoroughly cooked.

Clinical Diagnosis, Treatment, and Prevention.—See p. 543.

FASCIOLIASIS—INFECTION WITH FASCIOLA.

Fascioliasis is, properly speaking, distomatosis caused by species of the genus *Fasciola*. While the liver is the normal habitat for these worms, it occasionally happens that fascioles infest other parts of the body. In man fascioliasis is probably always due either (1) to a purely chance infection by the larvæ which then develop in the liver or, in rare cases, some other part of the body, as the lungs (p. 539), the eye (p. 556), or the veins (*Hexathyridium venarum*), etc.; or (2) to accidental infection with the adult worm, due, as Khouri (1904) has recently shown, to eating raw liver containing these parasites.

Geographical Distribution.—The common liver-fluke is reported with a very wide distribution but as the parasites on different continents are studied more carefully it is found that the infections alleged to be due to this species are specifically distinct, although generically identical. On account of these changes in ideas regarding classification this entire subject must be restudied. Europe is to be considered the type locality of *Fasciola hepatica* and the same parasite seems to occur in North America and Australia. It is also reported for Asia, Africa and South America.

Zoölogical Distribution.—This infection is reported from more animals than are probably actually infected with it but its normal hosts seem to be cattle, goats and sheep; it is also reported for many other animals.

The Parasite.—*Fasciola hepatica*¹ Linnæus, 1758, is a flat, leaf-like, spinose worm measuring 18 to 30 mm. (reported to 51 mm.) long by 4 to 13 mm. broad; the intestine, testicles, ovary, and vitellogene glands are profusely branched. Eggs, yellow-brown, oval, 130 to 145 by 70 to 90 μ , with distinct operculum, not containing embryo when oviposited.

Source of Infection.—Snails of the genus *Limnæa* (*L. truncatula*, *L. oahuensis*, *L. rubella*) form the intermediate host, and infection takes place normally by swallowing the encysted cercaria.

Frequency.—While this infection is rather common in cattle and sheep, especially those pasturing in marshy districts, it seems to be purely accidental in man. Not every case reported as *Fasciola hepatica* is to be accepted as such. One source of error is to mistake single segments of

¹SYNONYMS.—*Distoma hepaticum* (Linnæus) Abildgaard; *Fasciola humana* Gmelin, 1790; *Hexathyridium venarum* Treutler, 1793.

tapeworms for liver-flukes; the writer has seen several cases in which this had been done. Blanchard has carefully collated the authentic cases reported for man and Moniez has added several to Blanchard's list. The parasite has been reported for the liver by several observers. One recent case for Porto Rico is known to the writer; but while the parasite is a *Fasciola*, he believes that it represents a new species. Cases have been reported for the blood and in subcutaneous tumors.

Besides these cases, attention may be directed to the fact that the eating of raw liver infected with *F. hepatica* may be a much more serious matter than has heretofore been supposed and may cause in man a condition which, in certain localities at least, is apparently more common than is the presence of the common liver-fluke in the human liver.

Halzoun.—According to Khouri (1904), there exists in northern Liban, Syria, a disease known as "halzoun,"¹ which he attributes to *Fasciola hepatica* contracted through eating raw goat-liver infested with the parasite. His experiments upon rabbits, as well as clinical observations, indicate that the parasites attach themselves to the pharyngeal mucosa where they gorge themselves with blood after the manner of leeches; Khouri thinks that the parasites may secrete a substance which acts as a vasodilator. After gorging themselves with blood the flukes loosen their hold, reach the stomach, or are expelled with the vomit. There are two sets of symptoms; namely, congestive (a more or less intense œdematous congestion of the buccopharyngeal mucosa, of the larynx, nasal fossæ, tonsils, Eustachian tube, ear, conjunctivæ, and lips) and mechanical (dyspnœa, dysphagia, aphonia) resulting from the first phenomena. The mechanical symptoms are proportional to the severity of the congestive conditions; they are less constant but of more serious prognostic import. The symptoms appear a few minutes to an hour after eating the suspected liver and are localized in the cephalic region of the body; vomiting may result in expelling one or several worms and the severity of the attack varies with the number of worms present.

Subjective Symptoms.—After eating the infected raw liver, the patient experiences an itching sensation deep in his throat; soon he feels more or less malaise; the itching increases, extending to the ears and becoming painful; a buzzing in the ears follows and a sensation of auricular tension exasperates the patient. Two or three hours after onset the itching lessens; deglutition and dysphagia become painful; dysphonia develops and may extend to complete aphonia. The most alarming symptom is the dyspnœa, varying to orthopnœa in severe cases or asphyxia in fatal cases. The patient complains of a sensation of suffocation or of violent constriction of the throat, and of headache, usually frontal, which is sometimes extreme.

Objective Symptoms.—The aspect of the patient is typical; the face is congested, the lips thick, cyanotic and livid; an abundant saliva flows; the eyes are highly congested and there may be lachrymation; the conjunctivæ are injected and œdematous; photophobia and exophthalmia are common; the sight remains normal. The nose is large, red and shining; the pituitary mucosa is of an intense red-violet color, thickened, sometimes closing the nasal passages; usually it secretes a

¹Arabian word for spiral or snail.

yellowish, ropy mucus, sometimes very abundant. In severe cases the neck is swollen and œdematous; palpation shows a variable submaxillary and cervical adenopathy and a diffuse puffiness; the œdema invades the cervical cellular tissue, in serious cases extending to the clavicle. Examination of the throat shows congestion and a more or less intense œdema of the pharyngeal mucosa, of the palate and especially of the uvula and tonsils; the latter are considerably enlarged and, in severe cases, may meet in the median line, leading rapidly to asphyxia. Laryngoscopic examination shows an unusually narrowed superior larynx, of red-violet color, the vocal cords are slightly œdematous, but the opening of the glottis is not seriously restricted. There is rather an intense reddening of the external auditory canal and especially of the tympanum.

Somatic Symptoms.—The temperature usually remains normal but the pulse increases with the dyspnœa. Examination of the lungs and urine is negative.

Forms.—Besides the common form, described in the foregoing, one may distinguish light, grave, and fatal cases. In the light cases, dysphonia and distinct dyspnœa are not observed; the duration is short, varying from a few hours to two or three days. In the grave form the symptoms reach their maximum; the incubation is only five to twenty-five minutes; after ten to eighteen hours, the pharyngolaryngeal symptoms are intense; if the symptoms do not ameliorate by the end of thirty-six hours, to continue for four or five days in benign form, death is inevitable; usually this attack lasts five to eight days. In the fatal form the symptoms develop very rapidly.

Complications.—As complications may be found: abscess, especially in the external auditory canal and in the mastoid region, which may be treated surgically, suppurative otitis media, followed by perforation of the tympanum, and peripheral facial paralysis which disappears after eight or ten days.

Duration.—Attacks vary in length from a few hours to ten days. Most patients recover, death being exceptional.

Diagnosis.—As a rule this is not difficult but some cases may be confused temporarily with diphtheria, œdema of the glottis, cardiac or pulmonary dyspnœa and acute iodism.

Treatment.—Vomiting dislodges and expels the parasite, and should be encouraged; it is more effective if the stomach is well filled.

Prevention.—Avoid eating raw liver.

INTESTINAL DISTOMATOSIS.

The entire subject of intestinal distomatosis in man is one which needs a careful restudy. Undoubtedly the infections are much more common than is ordinarily assumed but we cannot as yet say for which infections man forms a normal, and for which an accidental host.

Geographical Distribution.—So far as the writer has records, intestinal distomatosis in man is reported only of Asiatic and African origin.

Zoölogical Distribution.—Similar infections, some of them generically identical with those found in man, are exceedingly common in other animals but of the infections which occur in man, only one (*Heterophyes*

heterophyes) is known to occur in other animals (cats, dogs and a fox).

The Parasites.—Intestinal distomatosis in man may be caused by the following flukes:

Fasciolopsis Buskii (Lankester, 1857).—This is the largest and perhaps the most important of the intestinal flukes of man; thus far it is known only for Asia (India, Assam, Siam, China, Straits Settlements, Sumatra), but Moore and Terril (1905) have reported one imported case in the United States. It measures 27 to 37 mm. (or even 75 mm., after Busk) long by 5.5 to 12 or 14 mm. broad, and 1.5 to 2 mm. thick. While not unlike the common liver-fluke (*Fasciola hepatica*) in superficial appearance, it can be easily distinguished from that form by its very large acetabulum and by its simple intestine. The eggs measure 120 to 130 by 77 to 80 μ with very delicate operculum. The life-history and source of infection are unknown.

Infection with this parasite is reported as being accompanied by indigestion, nausea, headache and severe diarrhœa with bloody stools. It is said to be expelled by thymol or with calomel.

Fasciolopsis Rathouisi (Poirier, 1887).—This trematode has been reported but once (Asia) and in this case it does not seem to have been definitely established whether the worm was in the intestine or in the liver. The patient is said to have had "severe body pains." The parasite measures 25 mm. long by 16 mm. broad; eggs ovoid, 150 by 80 μ . The life-history and source of infection are unknown.

Heterophyes Heterophyes (Siebold, 1852).—This is a minute trematode, 1 to 1.7 mm. long by 0.3 to 0.7 mm. broad, found in the middle third of the small intestine of man, dogs, and cats in Egypt and reported once for Japan. Its chief anatomical characteristic is the presence of a sucker-like disk surrounding the genital pore; the acetabulum is much larger than the oral sucker. The eggs are light brown, thick-shelled, oval, 20 to 30 by 15 to 17 μ with distinct operculum, and containing ciliated miracidium when oviposited. The life-cycle and source of infection are unknown. It seems to be entirely harmless in man (Looss).

Gastrodiscus Hominis (Lewis and McConnell, 1876).—This fluke, originally described as *Amphistoma hominis*, occurs in the cæcum and colon of man in India and has also been reported for East Indian immigrants in British Guiana. Braun is of the opinion that it is undoubtedly only a chance parasite in man and that its normal host is some Indian mammal. Indications are, however, not lacking that it is a more common parasite in man than has been supposed. It measures 5 to 8 mm. long by 3 to 4 mm. broad and when fresh is of a reddish color; the body is divided into an anterior, rather slender conical portion and a posterior flattened, ventrally concave disk with small ventral acetabulum at the posterior end. The eggs measure 150 by 72 μ and possess an operculum at the narrower end; the miracidium is not formed before oviposition. The life-history and source of infection are not known. Its medical importance is not established.

Cladorchis Watsoni (Conyngham, 1904) Shipley, 1905.—This is an 8 to 10 mm. long amphistome reported once from the small intestine of a negro boy from Adamawa, German West Africa.

VENAL DISTOMATOSIS—BILHARZIOSIS¹—BLOOD-FLUKE INFECTION.

Geographical Distribution.—Africa, Asia, Panama, Cuba and Porto Rico; probably more generally as a tropical and subtropical disease. Occasional cases, chiefly imported, are recorded for the temperate climates; several cases have been recognized in the United States.

Zoölogical Distribution.—The Asiatic blood-fluke is reported for cats as well as man. An infection occurs in the sooty monkey, which may perhaps be identical with the African blood-fluke. Generically identical but specifically distinct infections occur in horses, cattle and sheep.

The Parasites.—Bilharziosis in man may be due to either of two distinct species of trematodes, the African blood-fluke and the Asiatic blood-fluke.

The African blood-fluke, *Schistosoma hæmatobium*² (Bilharz, 1852), so far as records are published, is the more common of the two; it occurs chiefly in Africa and adjacent islands but extends to Persia, Arabia, India, Panama, Cuba and Porto Rico, and is occasionally found elsewhere. The male is 4 to 15 mm. long by 1 mm. broad; the sides are curved ventrally to form the gynæcophoric canal; the worm is armed with numerous spinose warts. The female is filiform, 15 to 20 mm. long and lives in the gynæcophoric canal of the male. The eggs are oval, 135 to 160 μ long by 55 to 66 μ broad, and are provided with a terminal,³ or lateral, subterminal spine, but not with an operculum.

The Asiatic blood-fluke, *Schistosoma japonicum*⁴ (Katsurada, 1904) has only recently been discovered (Japan, China, and the Philippines) and its frequency and distribution are not yet established. The male measures 7 to 12 mm. long by 0.53 mm. to 0.8 mm. broad; it is not armed with spinose warts; gynæcophoric canal present. The female measures 8 to 12 mm. long. The eggs 60 to 90 by 30 to 50 μ , and are not provided with the terminal or subterminal spine nor with an operculum.

The young worms live in the veins of the liver; in the portal vein there are but few young pairs; in the veins of the intestine and bladder-wall, paired flukes are numerous. Oviposition begins while the parasites wander from the portal vein to the pelvis, and eggs are deposited in various organs. The eggs with lateral spine are especially common in the liver and intestine. The ova (80 by 30 μ in utero) increase in size as they work through the tissues into the lumen of the intestine or of the bladder;

¹SYNONYMS.—Egyptian hæmaturia; endemic hæmaturia; bilharzian hæmaturia; bilharzia disease. See especially Looss, 1905, Manson, 1903, and Milton, 1902.

²SYNONYMS.—*Distomum hæmatobium* Bilharz, 1852; *Schistosoma hæmatobium* (Bilharz) Weinland, 1858; *Gynæcophorus hæmatobius* (Bilharz) Diesing, 1858; *Bilharzia hæmatobia* (Bilharz) Cobbold, 1859; *Bilharzia capensis* Harley, 1864.

³The position of the spine has given rise to considerable discussion, and the view has been advanced that the lateral spine may belong to a species of fluke which is distinct from that which produces the terminal spine. Looss (1905) has however recently shown that eggs with lateral spines are constantly formed at the beginning of sexual maturity and that the position of the spine is dependent upon the orientation of the egg in the ootype.

⁴SYNONYMS.—*Schistosomum japonicum* Katsurada, 1904, Aug. 13; *Schistosoma cattoi* Blanchard, 1905.

during this process they (or at least in *S. hæmatobium*) develop a ciliated embryo so that the miracidium is present when the egg is voided in the urine. Upon coming into water this embryo escapes from the egg-shell and it may live in water for thirty to forty hours.

Source of Infection.—From the miracidium in water to the time that the parasites are found in the veins of the liver, the life-history is unknown but evidence is rapidly accumulating which points to an infection directly through the skin. It seems possible, therefore, that an intermediate host is not necessary and that the alternating generations of the worm may develop in the liver. Analogy, however, seems to indicate that it is not yet time entirely to abandon the view, supported by many authors, that infection may perhaps take place through the drinking-water; but as observations accumulate this opinion does not seem to gain in strength. Some authors (Allen, Brock, Harley) assume direct infection through the urethra and anus.

Frequency.—Bilharziosis is much more common in males than in females and in rural districts than in cities. In a school near Cairo, Kautsky Bey found 98 cases in 124 boys examined, or nearly 80 per cent. infected; in two city schools, Engel Bey found 61 children, or 30.5 per cent. infected in 200 examined (Looss, 1905). Postmortem statistics indicate that it is present in quite one-half of the population of Egypt (Manson), and it is even more common in Uganda (Low). Several to 40 (Sonsino), or even to 300 (Kartulis) worms may be found in one patient.

Duration.—The incubation of the disease is about four to five months (Brock *et al.*), and it is said to last usually about two years (Milton, 1902); cases of longer duration are recorded in patients who have passed ova for nine (Sonsino) or fifteen years (Lortet) after leaving the infected area and some authors refer to cases of twenty to thirty years standing, although evidence is not presented that these were not due to repeated infection.

Symptoms—Course.—Bilharziosis is rarely acute (Griesinger); it usually stretches over years and if death occurs, it is, as a rule, from some intercurrent disease; Ruffer isolated the colon bacillus in the kidney of all the fatal cases he observed (Innes).

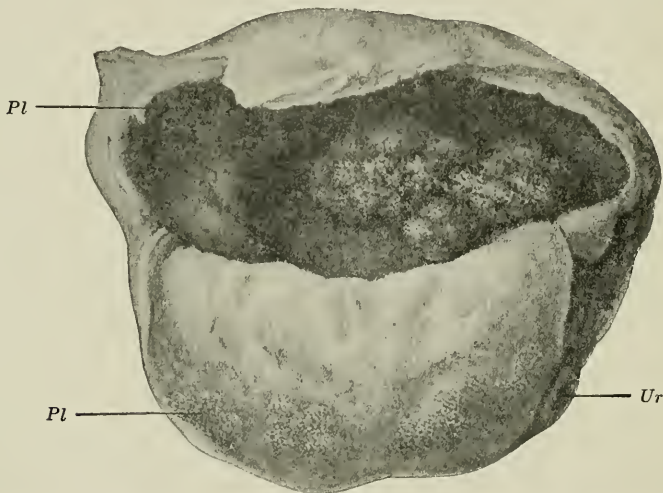
Types.—There are two chief forms of the malady but they may occur together. If the ova are confined chiefly to the urogenital system the prominent symptoms are: hæmaturia, pains in the lumbar region, left iliac fossa, thigh, or vulva, either spontaneous or on micturition; cystitis, vesical calculus, urinary fistulæ, vaginal tumors and nephritis may develop. If the ova are confined chiefly to the rectum the most prominent symptoms are: bloody stools, diarrhœa, prolapse of the rectum, and papilliform growths; thus far the Asiatic parasite has been reported only in connection with intestinal bilharziosis.

Hæmaturia.—This is the earliest and most prominent symptom. In many cases the patient suffers little or no inconvenience. The simple hæmaturia occurs chiefly in the better classes, the severer forms of bilharziosis occurring among persons who are subject to long and severe physical labor and almost exclusively among men. At the end of micturition a few drops of more or less pure blood are expelled and this may be the only symptom observed; frequently this is not noticed at the time but

attention is directed to it by blood stains on the shirt; the amount of blood lost is usually small, but in some cases more extensive; it may clot in the bladder and cause acute retention. Later, vague pains in the perineum, lumbar region, over the pubes, and a burning sensation in the urethra during micturition are experienced. At first the frequency of urination is not increased. All symptoms increase temporarily after excesses in diet or exercise, or during straining in defecation. The sediment of the urine contains red and white blood cells, epithelium, mucus and blood-fluke eggs.

The simple hæmaturia may be followed by *vesical catarrh*, increased micturition with severe pain and tenesmus, later by pronounced *cystitis*. The urine gradually loses its normal condition and becomes bloody, cloudy and offensive; loosened tissue from the bladder may clog the urethra; residual urine becomes constant; pyelonephritis and septic cystitis may result. Relatively soft vesical *calculi* may form and in

FIG. 37.



Bilharziosis of the bladder. *Ur*, urethra; *Pl*, flat, hard, encrusted elevations; note the cauliflower-like growth in the bladder. (Looss.)

infected geographical areas cases of vesical calculi commonly give a history of hæmaturia. Calculi may also form in the kidneys or ureters and cause hydronephrosis. Hypertrophy, contraction or dilatation of the bladder may occur. Pressure on the bladder causes pain; constipation is reported as general, and defecation causes emission of a few drops of blood from the urethra. In some cases there may be involvement of the prostate or of the vesiculæ seminales, causing spermatorrhœa, and in the latter event ova are found in the seminal discharge.

Urinary *fistula* is a frequent complication. This may form at any point near the genitalia but especially in the perineum near the scrotum; or on the posterior surface of the scrotum, where the fistulæ are usually multiple, and when the openings are numerous (up to 50 are recorded) some of these may be on the penis, over the pubes, near the anus, on the legs, etc.

According to Milton, all simple fistulæ spring from the urethra; most fistulæ take origin from the pubic side or roof of the urethra, a few from the perineal side or floor; most floor fistulæ are formed just in front of the bulb, but some may be found in the penile urethra. Urethral stricture is also encountered, especially (Milton) in case of floor fistulæ; the latter form from periurethral abscesses; the abscess discharge causes urethritis and a thickening of the wall; the urine escapes in drops and part of it enters the fistulæ. The urethra may become solid so that the catheter cannot be passed.

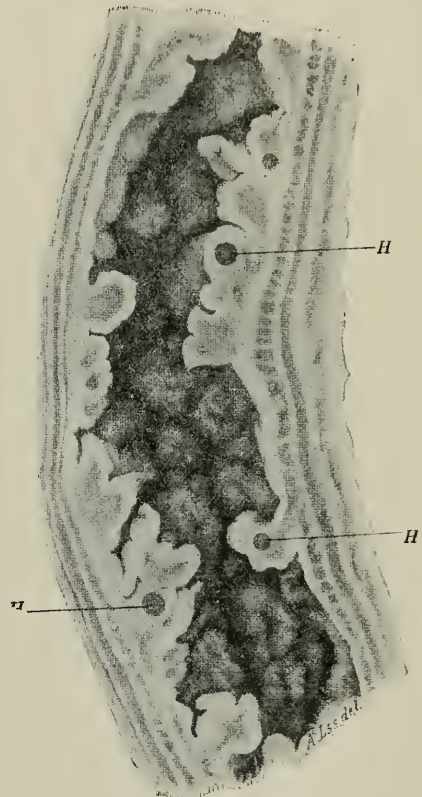
As a result of the suffering from these severer infections, the patient becomes anæmic, debilitated and wasted, and may succumb to some intercurrent disease.

When bilharziosis occurs in women it is usually as a hæmaturia. In vaginal bilharziosis there is subacute vaginitis, the mucosa thickens (especially on the posterior surface of the vagina) and becomes hard and dry and with longitudinal and transverse folds. Polypoid growths may be encountered, sometimes filling the entire vagina. The lesions may occur in the vagina without appearing in the bladder; bilharzia papilloma may be confused with epithelioma.

In rectal bilharziosis the mucous membrane becomes hypertrophied, excessively vascular, and of rich, red-velvet appearance; small or larger, simple or branching, soft, pile-like or coral-like growths are found from the sphincter up to the sigmoid flexure. There is excessive secretion of mucus and the patient feels as if his rectum were full and as if he wished to defecate. Little is passed, mixed with bloody mucus containing fluke-eggs. Repeated straining at stool causes prolapse of the rectum; at first this returns of itself but as time advances it must be helped back; finally the sphincter weakens and the rectum remains prolapsed; it becomes septic and may cause death.

Prognosis.—In case of light infection, the patient may not be inconvenienced. In simple uncomplicated cases, prognosis is not unfavorable but the possibility of new infection (since a careless patient is always a

FIG. 38.



Bilharziosis of the rectum. H, cavities filled with blood. (Looss.)

danger to himself as a source of infection) and the liability to septic infection, make bilharziosis a serious disease (Looss). In general, the prognosis is practically that of chronic cystitis depending upon an irremediable but not in itself fatal cause; much suffering may be looked for and, as a consequence, anemia and debility (Manson).

Clinical Diagnosis.—This should be made by microscopic examination of the urine and feces to find the eggs of the parasites. These will be found especially in the last few drops forced out at the end of micturition; or in the last drops of urine in the catheter. In old cases, however, the eggs may not be present in the urine; if necessary, the surface of the bladder may be scratched and the shreds examined for eggs or the polypoid growths in the rectum may be removed and examined (Manson).

To distinguish concurrent affections note: Chyluria (chyle in the urine, a large clot with oil granules and globules, and *Filaria* will be found in the blood); calculus (be careful not to mistake the hard, sandy, raised portions of the bladder-wall for stones); gonorrhœal cystitis (history); and enlarged prostate. Floor-fistulæ may be mistaken for stones in the urethra but the sound passes through and, as it is withdrawn, pus follows. In the rectum, distinguish bilharziosis from piles; large bilharzian tumors may resemble epithelioma or sarcoma.

Pathology.—It is generally admitted that it is the eggs rather than the worms that are of importance. These ova work their way into and through the tissues, particularly in the walls of the bladder, rectum, and vagina; they may also be found in the liver, lungs, heart, spleen, pancreas, kidneys, omentum, peritoneum, ligaments of the uterus, in gall-stones, and in the cutaneous epithelium. At first the eggs lie in the blood capillaries, but leaving these they collect in groups in the tissue, the infiltrated places appearing as yellowish to whitish specks, and as the lesion increases it forms a papular elevation containing eggs and minute dilated blood-vessels. These thickenings increase in size and may coalesce until the entire mucous membrane of the bladder becomes involved. Round, slightly projecting, dense patches of inflammatory thickenings, with granular surface and of hard consistency are seen, especially in the trigonum. The ova are especially numerous in the submucosa, less numerous in the mucosa, and still fewer in the muscularis and subserous connective tissue. After a certain age, the patches begin to break down, and even slough, giving rise to ulcers and crevices on their surfaces, which tend to retain a certain amount of urine to set up decomposition in it and favor deposition of its salts. In some cases the increase in the mucous membrane seems to be out of all proportion to the development of fibrous tissue and, in these cases, polypoid excrescences or more cockscomb-like tumors, sometimes ulcerated, may protrude into the lumen and may contain the worms as well as their ova. The bilharzia growths may cause retention of urine, resulting in dilatation of the ureters and involvement of the kidneys. The muscularis hypertrophies. The capacity of the bladder is decreased and its mucosa becomes covered with a bloody mucus containing numerous eggs. Carcinoma may develop.

Lesions similar to those of the bladder may be found also on the prostate, in the ureters (especially the lower third), less frequently in the pelvis of the kidney. The ureters may present constrictions and spindle-shaped or sacculated dilatations. Pyelitis, hydronephrosis, abscess, etc.,

may follow, and calculi (more important in the early stages of the disease) may form in the bladder, ureters or kidneys.

The vesiculæ seminales, vagina and cervix may also show a hyperplasia with a bloody discharge containing fluke eggs.

Rectal bilharziosis ranks second to the vesical form of the disease. The bilharzian growth may be mistaken for piles and may contain the adult worms as well as the eggs.

Blood.—Le Dantec (1904) gives the leukocyte count as follows: Polynuclears 57 per cent., mononuclears 35 per cent., eosinophiles 8 per cent.

Death is due to exhaustion from pain and want of rest, together with debility consequent on the constant hemorrhage, aided by poisoning from absorption of septic matter from the intestine, or to pyonephrosis, pyæmia, or uræmia.

Treatment.—No radical specific medical treatment is known at present, some authors even claiming that such attempts are undesirable and that efforts must be confined to palliating the effects of the presence of the parasites. Good results are claimed by some authors from daily doses of male fern (1 gm.—15 gr., t. i. d.), santonin, quinine or methylene blue (3 gr., t. i. d.), but the general opinion seems to be that treatment must be symptomatic for the cystitis and dysentery, and, further than that, operative if necessary. Milton warns against lithotomy if not absolutely necessary, but he had good results from lithotripsy; in case of very extensive changes in the bladder he uses double perineal drainage, by Cock's puncture, the drainage tubes being retained eight to ten days, but he says that the results cannot be foreseen, as the growths slough and the patient is likely not to survive; it may, however, simply be a question between draining and allowing the patient to suffer.

Hyperplasia in the vagina and cervix is treated by excision of thickened and infiltrated mucous membrane.

Perineal fistulæ are treated on general surgical principles; Milton uses "free and wide excision of the fistula and its surrounding tissues" and allows the wound to heal by granulation; he never ties a catheter in the urethra.

In rectal bilharziosis the irritation is allayed by local sedatives and astringent applications, as enemata of starch and opium, or solution of sulphate of copper. The rectal tumors are removed so far as possible. In case of high tumors Milton destroys them by swabbing for about a minute with chloride of zinc solution 1 to 10, then drying out the excess with cotton followed by washing with copious salt solution.

Operation on the prolapsed rectum, avoiding the sphincter, is more or less successful in fresh cases, but not in advanced cases of long standing. It is often difficult to decide whether excision of the prolapsed portion is justifiable.

Stimulants and spices should be avoided in the diet. Excesses of all kinds should be avoided and during exacerbations rest should be insisted upon.

Prevention.—Until the life-cycle and source of infection are better understood the best method of prevention cannot be definitely stated but it is probably one of the following and for the present both should be carried out: (1) Guard water against contamination with urine from bilharzia patients; water so guarded for two days may be safely used for

bathing purposes (Looss); (2) drink only filtered or boiled water, when in an infected district.

OPHTHALMIC DISTOMATOSIS.

Ophthalmic distomatosis has been reported for man on only two occasions:—

Monostomulum lentis (Gescheidt, 1833) is a trematode of uncertain systematic position which has been reported once, in Odessa, in the crystalline lens. Possibly it is an erratic liver-fluke.

Agamodistomum ophthalmobium (Diesing, 1850) is also of doubtful systematic position (possibly an erratic liver-fluke). It is reported once, in Dresden, between the crystalline lens and its capsule.

CHAPTER XXV.

TÆNIASIS—CESTODE INFECTION.

By CHARLES WARDELL STILES, PH. D., D. Sc.

Terminology.—*Tænia* was the original cestode genus (1758) and has served as the great collective genus of the tapeworms. It is now confined to cestodes of the type of *Tænia solium* but the term tæniasis may be conveniently retained to denote any cestode infection. We may have two kinds of tæniasis; namely, (a) intestinal infection with the tapeworm stage, or (b) somatic infection with the larval stage.

INTESTINAL TÆNIASIS—TAPEWORM¹ INFECTION.

The day is passed when a simple diagnosis of "tapeworm" is sufficient, for we now know that it may be a matter of importance, both to the physician and the patient, to establish what particular kind of tapeworm is present. Upon such determination may rest the question of the time of treatment, the precautions to be taken, and even—in exceptional cases—the risks to be run and the chances for complete recovery.

So far as is established, man seems to be the normal and sole host for the sexual stage of at least two of the large tapeworms, *Tænia saginata* and *T. solium*. Man, together with the dog, probably forms the normal host for a third large tapeworm (*Dibothriocephalus latus*). In common with rats and mice, man seems to have become a normal host for the dwarf tapeworm (*Hymenolepis nana*) although it is not absolutely established that the worm in man is exactly identical with that of the rodents; in fact, strong indications are not lacking that the worm (*H. n. fraterna*) in rats and mice is at least varietally, perhaps specifically, distinct from the worm in man.

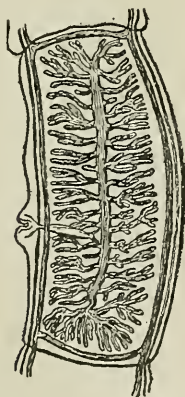
Occasionally, though rarely, as accidental host, man harbors the double-pored tapeworm (*Dipylidium caninum*) of dogs and cats, the flavopunctate tapeworm (*Hymenolepis diminuta*) of rats, and the lanceolate tapeworm (*H. lanceolata*) of ducks and geese. The other tapeworms reported for man are: *Tania confusa* (twice, in the United States), *T. hominis* (once, in Aschabad), *T. africana* (two specimens from East Africa), *Davainea madagascariensis* (occasionally in the tropics), *D. asiatica* (once in Asiatic Russia), *Dibothriocephalus cordatus* (Greenland), *Diplogonoporus grandis* (twice, in Japan); but too little at present is known of

¹For keys to and specific diagnoses and full synonymy of the various tapeworms of man see Stiles, 1906, pp. 1-104, Figs. 1-160. *Bulletin 25*, Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, Washington.

the occurrence of these species to permit a definite judgment as to whether man is their normal or simply an accidental host, except perhaps in the case of *Dib. cordatus* for which man seems to be an accidental host. Interesting as the ten last-named infections are and without expressing any adverse opinion as to their importance when they do occur, it may be said that from a clinical point of view our present knowledge of the adult tapeworms in man is based chiefly upon three large species (*Dibothriocephalus latus*, *Tania solium*, *T. saginata*), and one small species, (*Hymenolepis nana*). Of these the average practitioner in Australia, England and North America will come in contact especially with the fat tapeworm (*T. saginata*); he will doubtless meet infections with the dwarf tapeworm (*Hymenolepis nana*) but will usually fail to recognize them, although in some parts of the United States he will probably have five or more cases of this parasite to one of the fat tapeworm; it is the exception that the pork-measle or armed tapeworm (*T. solium*) is found; while probably not one physician in a hundred, in Australia, England and North America, has seen an infection with the broad tapeworm (*Dibothriocephalus latus*), and if he does see such, it may be chiefly imported cases among Russians, Swedes, Finns, Germans or in persons who have visited the more infected European or Asiatic localities.

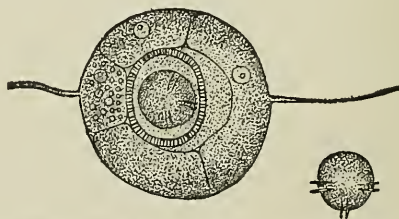
All four of these species present certain points which should be borne in mind. The pork-measle tapeworm, though not common, is by far the most dangerous. The dwarf tapeworm is the most common in some localities, though its frequency in others is not established; although it is very small it may occur in large numbers and produce severe symp-

FIG. 39.



Gravid segment of beef-measle tapeworm (*Tania saginata*), showing lateral branches of the uterus, enlarged. (Stiles.)

FIG. 40.



Egg of beef-measle tapeworm (*Tania saginata*) with thick egg shell (embryophore), containing the six-hooked embryo (onchosphere), enlarged. (Leuckart.)

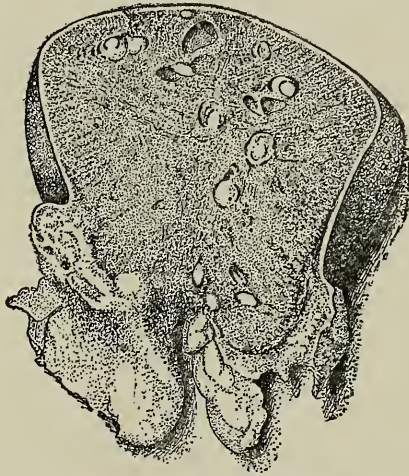
oms. The fat tapeworm is the most common of the larger forms; it may produce severe symptoms, is sometimes difficult to expel, but is not dangerous as compared with *T. solium*. The broad tapeworm may be associated with a more or less severe anæmia.

The Fat Tapeworm.—*Tania saginata* Goeze, 1782.—**Geographical Distribution.**—Practically cosmopolitan.

Zoölogical Distribution.—The adult is known only for man. The larva (*Cysticercus bovis*) is found in cattle; it is also reported by several authors for man but doubts arise regarding the determinations; experiments to grow it in apes, dogs, goats, hogs, rabbits, and sheep have been negative but it is reported that Heller succeeded in infecting a sheep and that Zenker and Heller were able to infect young goats.

The Parasite.—The fat or unarmed tapeworm, *Tænia* (*Tæniarhynchus*)¹ *saginata*,² is one of the largest known cestodes, attaining a length of about 4 to 8 or 10 meters; the head is without hooks; there may be more than a thousand segments present; only two ovaries are found in each mature segment; the uterus in the gravid segments has 15 to 35 slender dichotomous lateral branches each side of, and shorter than, the median stem; genital pores lateral (marginal), irregularly alternate; terminal segments attain 16 to 25 mm. long by 4 to 7 mm.

FIG. 41.



Section of a beef tongue heavily infested with beef measles, natural size. (Stiles.)

broad; eggs with thick, dark, radially striated embryophore ("inner shell," or "shell" in most medical works) 30 to 40 by 20 to 30 μ .

Source of Infection.—This parasite is obtained through eating beef, especially the tongue and the muscles of mastication, infected with

¹In zoölogical writings, a capitalized name inserted in parentheses between the generic and the specific names denotes the subgenus. The present genus, *Tænia*, for instance, may be divided into the subgenera: *Tænia*, type *T. solium*; *Tæniarhynchus*, type *T. saginata*; and *Multiceps* Gœze, 1782, (*Cænurus* 1808) type *T. cænurus*. Subgenera are used in zoölogy for several purposes: Their chief use is to enable the classification of species into groups to which generic rank is not given; another use of subgenera is to foreshadow probable changes in the classification. When a genus is divided into subgenera, it is not necessary to cite the subgeneric name when referring to the species. Thus, *Tænia saginata* is as valid a citation as *Tænia* (*Tæniarhynchus*) *saginata*.

²SYNONYMS.—*Tænia solium* Linnæus, 1758 pro parte; *T. mediocanellata hominis*, seu *T. mediocanellata* seu *T. zittaviensis* Küchenmeister, 1852; *T. inermis* Moquin-Tandon, 1860.

Cysticercus bovis.¹ Cattle become infected by swallowing the embryo (onchosphere), encased in its embryophore, in their food or in water contaminated directly or indirectly with infected human faeces.

Frequency.—This is by all means the most common of the large tapeworms of man in North America and Europe (except in certain regions where *Dibothriocephalus latus* abounds) but it will doubtless gradually decrease in frequency because of the meat inspection and cold storage of beef. It is reported as exceedingly common in certain localities of Africa and Asia. It is more common in females than in males and while it may be present in patients of almost any age it is more common in people between twenty and forty. Usually only one specimen is present in a patient but infections with from 1 to 59 worms are reported.

Duration.—Beyond the fact that persons may harbor this worm for a number of years, the exact longevity of this species is not established; considering the method by which the segments are formed, the age of the worm seems to be, theoretically, potentially almost indefinite.

Special Medical Features.—The fat tapeworm is not only more common than *Tania solium*, but the general consensus of opinion seems to be that it is more difficult to expel, despite the absence of hooks from the head. While clinical reports seem to show that anæmia is more likely to result from *T. saginata* than from *T. solium*, and less likely than from *Dibothriocephalus latus*, the fat tapeworm is really of much less importance than *T. solium*, for it does not combine with it the danger of cysticercosis (p. 574) which we may find associated with infection with *T. solium*. Hence, if treatment is not convenient at the time of diagnosis (as in case of pregnancy or because of important business engagements) this can be postponed until a more convenient time without any special danger to the patient.

Differential Diagnosis.—It is unwise for the physician to trust to distinguishing *Tania saginata* from *T. solium* on the microscopic examination of the eggs found in the faeces. The author has examined the adult worms which various persons have positively determined by this method as being *T. solium* and in every case thus far the parasite has proved to be *T. saginata*. It is also unwise to rely only upon the form of the segments. A safer plan is to press the discharged segments between two pieces of glass, hold the preparation to the light, and count the lateral branches of the uterus. If the head is found, determine the presence (*T. solium*) or absence (*T. saginata*) of hooks.

Prevention.—Proper disposal of human faeces should prevent the infection of cattle; a proper system of meat inspection² prevents the infection of man; the cysticerci in beef die within three weeks after the death of the steer, so that beef which has been killed for twenty-one days will not transmit this parasite; thorough cooking or thorough salting of the meat also kills the parasite.

Tænia (Tæniarhynchus) africana Linstow, 1900, is a species closely allied to *T. saginata*; only two specimens have been found—in the negro in German East Africa. The parasite attains 1.4 meters in length; scolex unarmed; segments about 600 in number, always broader than

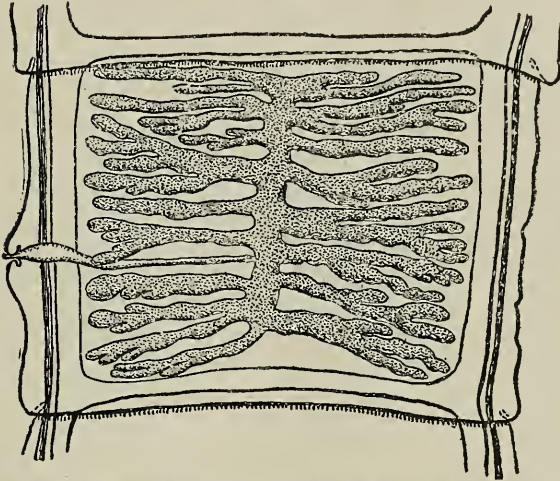
¹SYNONYMS.—*Cysticercus tæniæ saginatae* Leuckart; *C. bovis* Cobbold, 1866; *C. tæniæ mediocanellate* Knoch, 1868; *C. inermis* of various Germans and others.

²See Stiles, 1898, pp. 77-83. *Bulletin* 19, U. S. Bureau of Animal Industry.

long, attaining 7 mm. in length by 12 to 15 mm. in breadth; uterus with 15 to 24 simple (not dichotomous) branches each side of, and longer than, the median stem; embryophore 31 to 39 by 33.8μ . The life-cycle and source of infection are unknown but the zebu has fallen under suspicion as possibly representing the intermediate host.

Tænia (*Tæniarhynchus*) *hominis* Linstow, 1902 was found once, in Aschabad, in a girl. The parasite measured 70 mm. long by 1.11 to 1.97

FIG. 42.



Gravid segment of pork-measle tapeworm (*Tania solium*), showing the lateral branches of the uterus, enlarged. (Stiles.)

mm. broad. The scolex possesses a rudimentary rostellum without hooks; suckers directed postero-anteriorly; caudad of suckers a circular ridge is present. The genital organs were not developed, but von Linstow considers that the indications are that this worm may attain as great size as *T. saginata*.

The Pork-Measly Tapeworm.—*Tania solium*.—**Geographical Distribution.**—Practically cosmopolitan, following the hog.

Zoölogical Distribution.—Adult known only for man; experiments to grow it in a monkey (*Macacus cynomolgus*) and in dogs, guinea-pigs, hogs and rabbits have been negative. The larva (*Cysticercus cellulosæ*¹) is found, especially, in hogs; it is said that it may, occasionally, occur in sheep, and it will develop in young dogs.

The Parasite.—The armed or pork-measle tapeworm, *Tania* (*Tania*) *solium*² (Linnaeus, 1758) is slightly smaller than the fat tapeworm; it does not usually measure over 2 to 3.5, 6, or 8 meters in length; the head is armed with a rostellum bearing a double row of hooks, of larger and smaller size, 22 to 32 in number; genital pores lateral (marginal), irregularly alternate; mature segments contain 3 ovaries, due to

¹SYNONYMS.—*T. cellulosæ* Gmelin, 1790; *C. cellulosæ* (Gmelin) Rudolphi, 1808.

²SYNONYMS.—*Tania solium* Linnaeus, 1758 (after elimination of *T. saginata* and *T. hydatigena*).

the fact that the ovary on the pore-side of the segment is divided; the segments may attain 10 to 12 mm. in length, by 5 to 6 mm. in breadth; 800 to 900 segments may be present; in gravid segments, the median uterine stem possesses 7 to 15 lateral dichotomous branches each side; "eggs" (embryophore) very similar to those of *T. saginata*, 31 to 36 μ in diameter.

Source of Infection.—This parasite is obtained by eating under-cooked, or under-pickled, or under-cured pork or wild-boar meat. The hogs become infected by eating human faeces containing the egg with its enclosed embryo, or from food or drink contaminated with these eggs. To build a privy over the pig-pen, as one repeatedly sees in rural districts, means the formation of an endless chain in the biology of this worm.

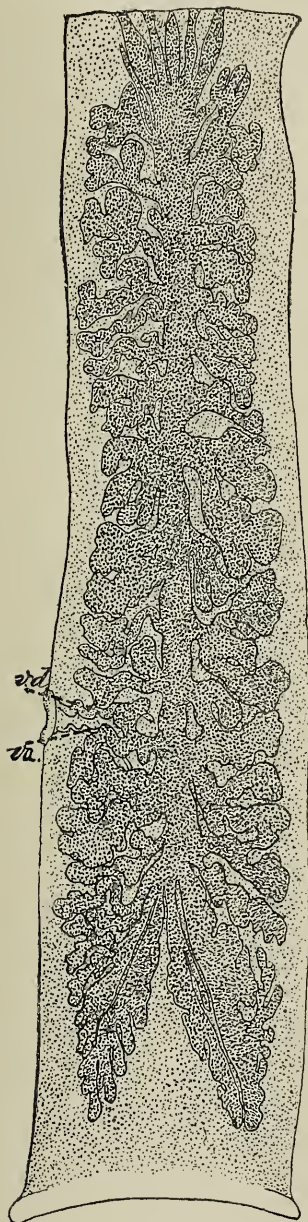
Frequency.—As has been shown by Leidy, Osler, and the writer, this is certainly a rare parasite in the United States and Canada, despite the statements of several authors (possibly due to Weinland) to the contrary. Of 300 tapeworms from man examined by the author from 1891 to 1895, 297 were *T. saginata*, and none *T. solium*. Of 28 tapeworms recently (1905) examined by him in two New England Museums, 23 were *T. saginata* (several were labelled *T. solium*), 4 were *Dibothriocephalus latus*, and 1 was too poor to determine. From 1891 to 1905, the only authentic specimen of *T. solium* sent to the writer came from Germany. Osler reports 76 cases of the cysticercus in hogs out of 1,000 examined in Montreal; and the writer has seen several American cases of cysticercosis in hogs and man due to this species; so that there can be no doubt regarding its occurrence in this country. Perfectly authentic cases of *T. solium* in man have been recognized in the United States. However the average *T. solium* mentioned in American literature is undoubtedly *T. saginata*. *T. solium* is said to be rather common in Panama. The infrequency of the pork tapeworm in America is due probably to (a) national culinary habits, (b) the curing methods, and (c) the federal meat inspection. In Europe, *T. solium* is decreasing in frequency, because of the meat inspection. It is not found among orthodox Jews, or among other people who do not eat pork. It is especially likely to be found in people (as of Saxon and East Prussian origin, but not of West and South German origin) who eat raw or rare pork. It may be found in patients of almost any age, but appears to be more common in people between twenty and forty years.

Duration.—The longevity of the individual parasite is not definitely established, but it can doubtless live for years (ten to fifteen or more).

Special Medical Features.—While less likely, according to clinical reports, to result in anæmia than is either *Tania saginata* or *Dibothriocephalus latus*, the fact must constantly be held in mind that *Tania solium* is dangerous especially because of the possibility of its producing cysticercosis (see p. 574). On account of this danger, it is much more important to treat promptly the infection with *T. solium* than the infection with any other tapeworm. Further, not only is a patient with *T. solium* a constant danger to himself, but also to other members of his family, and especially to any one occupying the same bed with him. Accordingly, a patient with *T. solium* should never sleep in bed with another person, not only between the time of diagnosis and treatment, but also until a definite cure is thoroughly established. He should also be warned to be

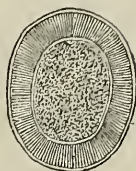
unusually cautious about his personal habits, relative to washing his hands and cleaning his finger-nails.

FIG. 43.



Gravid segment of *T. confusa*, to show the uterus. $\times 6$. (Guyer)

FIG. 44.



Onchosphere surrounded by embryophore, from uterus. $\times 660$. (Guyer.)

Prevention. — Fæces from infected patients should be so disposed of that they can not infect hogs; hogs heavily infected (severe hog-measles, acute cestode tuberculosis) should be destroyed, but if the infection is very light no valid hygienic objection can be raised against eating the meat *in case it is thoroughly cooked*; cold-storage is not so effective against this parasite as it is against *Cysticercus bovis*, for *C. cellulosæ* has been found to be alive twenty-nine days after its host was slaughtered.

Tænia (*Tænia*) *teniaeformis* (Bloch, 1780) is a tapeworm which cats contract from eating mice containing *Cysticercus fasciolaris*. Krabbe thinks its occasional presence in man is possible, because in Jutland hashed raw mice are occasionally eaten as a remedy for retention of urine. No authentic case of such infection seems to be reported as yet.

Tænia (*Tænia*) *pisiformis* (Bloch 1780), is a tapeworm which dogs contract by eating rabbits infected with *Cysticercus pisiformis*. Vital (1874) reports this tapeworm in man, but legitimate doubts may arise regarding the correctness of the zoological determination, especially in view of the fact that Galli-Valerio (1898) was unable to infect himself with this species experimentally by swallowing the larval stage.

Tænia (Subg.?) confusa Ward, 1896 has been found in Lincoln, Nebraska. It attains 5 to 8 meters in length; head unknown; segments may attain 27 to 35 mm. long by 3.5 to 5 mm. broad, greatest breadth 8 to 10 mm.; ovaries 2, distinctly reniform; uterus with 14 to 18 short, thick, dichotomous lateral branches each side of median stem; eggs 39 by 30 μ .

Thus far little is known regarding the history and clinical significance of this American tapeworm, which should be looked for especially in the Northwest.

The Dwarf Tapeworm.—*Hymenolepis nana*.—**Geographical Distribution.**—In North America this parasite has been found from Pennsylvania to Texas, but its distribution is probably much more extensive. It is also reported for South America, Europe, Asia, Africa, and is probably more or less cosmopolitan.

Zoölogical Distribution.—Several authors (Grassi, Lutz, Ransom, and others) consider *Hymenolepis nana fraterna*¹ Stiles, 1906, of rats and mice identical² with *H. nana* of man, but other authors (Moniez, Braun, Looss) are inclined to doubt this identity. Grassi and Looss were unable to transmit the parasite of man to rats.

The Parasite.—*Hymenolepis nana*³ (Siebold, 1852) is the smallest tapeworm known for man. It measures 5 to 45 mm. long by 0.5 to 0.9 mm. in maximum breadth, and is composed of 100 to 200 small segments. The rostellum is armed; there are 3 testicles to each segment, and the genital pores are unilateral. The eggs have 2 distinct membranes: outer membrane 30 to 60 μ in diameter; inner membrane 16 to 34 μ , presenting at each pole a more or less conspicuous mammillate projection provided with filamentous appendages. The adults are found especially in the upper two-thirds or three-fourths of the ileum.

Source of Infection.—*Hymenolepis nana fraterna* develops in rats without any intermediate host; the eggs escape in the feces, and when swallowed, the onchosphere (embryo) bores into the villi of the intestine, where it develops within a few days into a larva (cercocystis); the latter reaches the lumen of the intestine and develops into the adult strobila. If the form in rats is identical with *H. nana*, man probably receives his infection from food soiled by the excrements of rats and mice. The large number of specimens sometimes found in man would at least indicate that *H. nana* probably develops in the manner described for the form that occurs in rats; auto-infection seems highly probable.

Frequency.—This parasite⁴ is unquestionably much more common than is generally supposed, and indications are not lacking that, in certain

¹*H. murina* (Dujardin, 1845).

²From the hygienic point of view this assumption must be made until the zoölogical points in question are definitely settled; applied zoölogy is of course dependent upon theoretical zoölogy, but in doubtful cases we must be more conservative in applied than in abstract science. The writer considers the form from rodents entitled to at least subspecific rank.

³SYNONYMS.—(?) *Tænia murina* Dujardin, 1845 (not *T. murina* Gmelin, 1790; *Cysticercus fasciolaris* Rudolphi); *T. nana* Siebold, 1852 (not VanBeneden, 1858); *Hymenolepis nana* (Siebold) Blanchard, 1891; *H. murina* (Dujardin) Blanchard 1891; "*Hymenolepsis*" *nana* of Osler, 1895, and other authors (misprint)

⁴For a complete discussion, in English, of the three species of *Hymenolepis* which occur in man, together with summary of cases, see Ransom, 1904, pp. 1-138, figs. 1-130. *Bulletin* 18, Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, Washington.

parts of the world, at least, it is the most common tapeworm of man. The author found it in 4 cases (2.5 per cent.) of about 160 persons examined between Richmond, Va., and Florida; his assistants found it in 6 cases (4.8 per cent.) of 123 children in a Washington orphanage. Calandruccio estimates that in Sicily 10 per cent. of the children are infected. In Germany, the parasite does not appear to be common, so far as can be judged from existing statistics. It has been found in patients from under five to over fifty years of age but is more common in children

FIG. 45.



Head and strobila of dwarf tapeworm, (*Hymenolepis nana*), enlarged. (Leuckart.)

FIG. 46.



Egg of *Hymenolepis nana* as seen in fresh feces, enlarged. (Ransom, from Stiles.)

from five to ten years old, and in boys than in girls. Crowded conditions, as in dormitories of orphan asylums, seem to be favorable to the spread of the parasite, which is, further, more common in poorer than in well-to-do families. From one or two specimens to several thousand worms may be found in a patient.

Duration.—The length of life of the individual parasite is not definitely established, but infections have been reported as lasting from two months to two and one-half years.

Special Medical Significance.—Although this is a small tapeworm it seems a serious error to assume that it is of no significance. Light infections do not appear, *per se*, to be of much symptomatic importance, but they may lead to heavy infections productive of pronounced symptoms. See p. 569. The local lesions produced by the parasite seem to be slight, and Mingazzini sug-

gests that the symptoms are due to a toxin eliminated by the worm.

Treatment.—Male fern is the only remedy which has thus far been useful in expelling this worm, while cusso, kamala, santonin, thymol, and pomegranate have failed in the cases in which these drugs were tried.

Prevention.—On the assumption that *H. nana* in man is specifically identical with the small tapeworm of rats and mice, the most important point in prevention lies in protecting food from these rodents. If a person is found to be infected, he should occupy a separate bed until fully cured.

Hymenolepis diminuta¹ (Rudolphi, 1819), the flavopunctate tapeworm of rats, occasionally occurs in man. It measures 10 to 60 mm. long by 2.5 to 4 mm. in maximum breadth, and is composed of 800 to 1,300 segments. The head is unarmed; 3 testicles are present in each segment, and the genital pores are unilateral. The eggs are round to oval; the outer membrane (56 to 80 μ) may be radially striated; the inner membrane measures 24 to 40 by 20 to 36 μ . The larval stage lives in insects, such as the larva and adult of meal moths, ear-

FIG. 47.

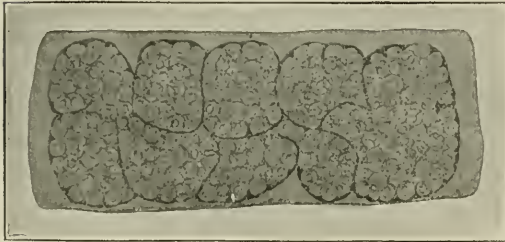
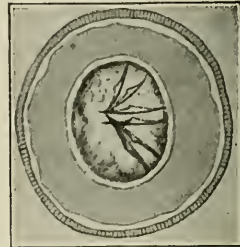
Gravid segment of *H. diminuta*, enlarged. (Grassi.)

FIG. 48.

Egg of *H. diminuta* from man, greatly enlarged. (Bizzozero.)

wigs and in adult beetles. Of the 12 cases thus far reported for man, 3² are recorded for the United States, 2 for South America, and 7 for Europe.

Hymenolepis lanceolata³ (Bloch, 1782), the lanceolate tapeworm of ducks and geese, has been reported once (in Germany) for man. This worm is supposed to pass its larval stage in small crustaceans belonging to the family *Cyclopidae*.

Davainea madagascariensis (Davaïne, 1869) is known only for man, and has been reported 9 or 10 times (Comoro Islands, Mauritius, Siam, Nossi-Be, British Guiana), chiefly in children. It measures 25 to 30 cm. long and is composed of 500 to 600 segments which attain 2 mm. long by 1.4 mm. broad; head with large round suckers, rostellum with 90 hooks; genital pores unilateral; calcareous corpuscles present; about 50 testicles present; eggs with 2 clear shells, the outer possessing 2 mammillate projections; eggs collect in 300 to 400 egg-balls. The intermediate host is unknown but Blanchard has suggested that possibly the cockroach (*Blatta orientalis*) plays this role.

Davainea asiatica (Linstow, 1901) was found once in Aschabad, Asiatic Russia. The scolex is unknown, but the anatomy of the fragment indicates that the worm is a *Davainea*; it measures 298 mm. long by 0.16 to 0.99 mm. broad and possesses about 750 segments; calcareous corpuscles absent; genital pores unilateral; ventral canals very large; all

¹SYNONYMS.—*Tenia diminuta* Rudolphi, 1819; *Hymenolepis flavopunctata* Weinland, 1858; *Hymenolepis diminuta* (Rudolphi, 1819) Blanchard, 1891; "*Hymenolepsis*" *flavopunctata* of Osler, 1895, and other authors (misprint).

²Two additional cases, recently recognized in Arkansas and in Nebraska, are known to the writer.

³SYNONYMS.—*T. lanceolata* Bloch, 1782; *Hymenolepis* (*Dilepis*) *lanceolata* (Bloch, 1782) Weinland, 1858.

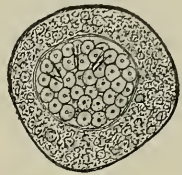
genital organs are developed at 70 mm. from anterior end. The eggs collect in 68 to 70 egg-balls.

Dipylidium caninum¹ (Linnæus, 1758), the double-pored dog-tape-worm, has been reported for man (chiefly children), about 25 times, at least 2 of the cases being recorded in American literature. It measures 15 to 30 cm. in length by 1.5 to 3 mm. in maximum breadth. The head is armed with hooks and there are 2 sets of genital organs to each segment. It is a very common parasite in dogs and cats, and the larval stage lives in dog lice (*Trichodectes canis*), the dog flea (*Ctenocephalus canis*) and the human flea (*Pulex irritans*).

The Broad Tapeworm.—*Dibothriocephalus latus*.—**Geographical Distribution.**—The general rule may be laid down that this parasite is more common in the vicinity of large bodies of water (as in lake regions) than in regions of other topography. It is reported as especially common in Europe for the Russian Baltic provinces, Finland, Sweden, Denmark, North East Prussia, Switzerland, and Northern Italy, but it occurs also elsewhere, as in Belgium, Holland, Ireland, Northern France, etc. It is common in Japan and Turkestan, and is reported for Iceland, N'gami Lakes (Africa), Madagascar, South Africa, and the United States. It bids fair to become almost cosmopolitan, following the fresh water fish diet.

Zoölogical Distribution.—The adult worm occurs in man, cats, dogs, and foxes (rare). The larval stage (a "plerocercoid") attains a length of 30 mm. and is found in the muscles and various organs of fresh-water fish, particularly in the pike, ling or burbot, perch, and several members of the salmon family.

FIG. 49.



Egg of *Dipylidium caninum*. Note the six hooks in the embryo, greatly enlarged. (Stiles.)

FIG 50.



Gravid segment of *D. latus*, showing the rosette uterus in the median line. $\times 6$. (Leuckart.)

The Parasite.—*Dibothriocephalus latus*² (Linnæus, 1758) attains 2 to 9 or 10 meters in length by 20 mm. in maximum breadth; it is usually grayish-yellow to brown in color, and composed of 3,000 to 4,200 segments,

¹SYNONYMS.—*Tania canina* Linnæus, 1758; *T. moniliformis* Pallas, 1781; *T. cucumerina* Bloch, 1782; *T. elliptica* Batsch, 1786; *T. (Dipylidium) cucumerina* of Leuckart, 1863.

²SYNONYMS.—*Tania lata* Linnæus, 1758; *T. vulgaris* Linnæus, 1758; *Bothriocephalus latus* (Linnæus) Bremser, 1819; *Dibothrium latum* (Linnæus) Diesing, 1850; *Bothriocephalus cristatus* Davaine, 1873; *Dibothriocephalus latus* (Linnæus) Luehe, 1899.

which are usually broader than long, especially in the anterior two-thirds of the strobila; posterior segments become quadrate or even longer than broad, and are especially characterized by the rosette spot (uterus) in the centre; genital pores ventromedian; eggs 68 to 71 by 45μ , with distinct operculum; laid during segmentation.

Source of Infection.—This tapeworm is contracted by eating raw or under-done fish, see p. 567.

Frequency.—About 30 cases of infection with this parasite have been recognized for the United States, chiefly among foreigners. In some parts of Europe it is reported as the most common tapeworm of man, the frequency varying from 0.8 to 10, 20 and, locally, even to more than 50 per cent. of the population. In Turkestan and Japan it is the most common tapeworm of man. Very probably it will become more commonly known in the United States, for now that special attention has been recently directed to it in several American medical journals, it will be more frequently recognized and further it is highly probable that immigrants will infect the fish of some of our lake regions. It is observed more commonly in adults but may develop in persons of any age.

FIG. 51.



Egg of *D. latus*. $\times 400$.
(Looss.)

Duration.—The growth, after infection, is very rapid. According to Braun, the average daily increase for the first five weeks is 31 to 32 segments, involving 8 to 9 cm. increase in length; Zschokke found the average daily increase in length to be 5.2 to 8.2 cm.; eggs may appear in faeces twenty-four days after infection. Cases have been recorded of fourteen years duration (Mosler).

Special Medical Significance.—The special medical significance of infection with the broad tapeworm is the tendency to development of a severe anæmia (Reyher, 1886, etc.) resembling pernicious anæmia. Retinal hemorrhages have been reported in 50 per cent. of certain cases studied. This anæmia is attributed by most authors to a toxin, supposed to be eliminated by the parasite, and a lethality as high as 16 per cent. has been reported by one author. Schauman (1894) found the red corpuscles reduced to an average of 1,311,000 (in males) and 1,273,000 (in females) in 38 out of 72 cases; he also found elevated temperature (99° to 104° F.) in 81 per cent. of his cases; the pulse is usually full, often accelerated to 90 or 120.

Clinical Diagnosis.—There should be little or no difficulty in diagnosing cases of this infection. As the uterus has a special uterine pore, eggs are constantly discharged from gravid segments and may be found in the faeces by microscopic examination. The segments show a tendency to be passed in small chains and ought not to be confused with those of the other tapeworms found in man.

Prevention.—Faeces of persons harboring this worm should be cared for in such a way that the eggs contained therein do not gain access to fresh-water streams or lakes. Thorough cooking of fish will protect man from infection.

Ward (1906) has recently reported, but not yet described, a new bothriocephalid tapeworm as occurring in the United States.

Dibothriocephalus cordatus¹ (Leuckart, 1863) is reported in Greenland for man, dogs, bearded seal, and walrus. Its reported introduction into the vicinity of Dorpat and Berlin (Prussia) is based upon an error of zoölogical determination. It measures 80 to 115 cm. long with a maximum breadth of 7 to 8 mm. and is composed of about 600 segments; uterus with 6 to 8 lateral loops each side; the head is heart-shaped; neck absent; eggs 75 to 80 by 50 μ . It is probably contracted by eating fish.

Diplogonoporus grandis (Blanchard, 1894) has been found twice in Japan. It may attain 10 meters in length, by 25 mm. in maximum breadth. It is similar to *Dibothriocephalus*, but with 2 complete sets of genital organs to each segment. The eggs are brownish, rather opaque, 63 by 48 to 50 μ . The source has not been demonstrated but infection probably takes place through eating fish.

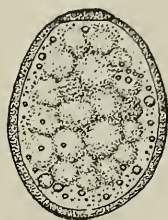
Ashford, King and Gutierrez (1904, p. 92) report 1 case of this infection in Porto Rico but as the determination was made solely upon the eggs in the stools while the adult parasite was not seen, legitimate doubts may arise regarding the correctness of the zoölogical determination.

Symptoms.—Irregular appetite with occasional pains extending from the region of the stomach to the back; intestinal disturbance indicated by diarrhoea, colic, and constipation; anæmia; poorly nourished condition, weakness, and inclination to faint.²

General Symptoms of Intestinal Tæniasis.—In connection with the various species of tapeworm found in man, reference has been made to the special medical significance of each form. In regard to the general clinical picture presented by patients harboring tapeworms, one noted clinician has remarked that its chief characteristic is its lack of anything characteristic. That a person may harbor a tapeworm, especially one of the smaller species, and be unaware of the fact, cannot be doubted; and this fact has led more than one person to minimize the importance of cestode infection. On the other hand, that tapeworm infection may result in severe symptoms is equally well established, for in numerous cases such symptoms have disappeared with the expulsion of the parasite; and this fact has led some observers to exaggerate its importance. We shall probably follow a justified mean between these extremes if we consider that the severity of the symptoms varies with the species of tapeworm present, with the number of the parasites, and with the age and general physical and nervous condition of the infected person. The injury is attributed to the following factors in particular: mechanical obstruction, injury or irritation to the intestinal mucosa, loss of food which goes to the parasite instead of to the host, and toxins produced by the worms.

The appetite varies; it may be decreased, increased to a point of insatiability or the two conditions may alternate; Hirsch reports loss of appetite in 6 per cent. of cases, bulimia in 10 per cent., capricious

FIG. 52.



An egg of *D. grandis* taken from the uterus. $\times 440$. (Ijima & Kurimoto.)

¹ SYNONYM.—*Bothriocephalus cordatus* Leuckart, 1863.

² For an account of this worm, in English, see Stiles and Taylor, 1902, pp. 43-47 figs. 22-28. *Bulletin* 29, U. S. Bureau Animal Industry.

appetite in other cases;¹ Seeger records irregular appetite or bulimia in 31 per cent. (selected cases).

Salivation is often mentioned; Hirsch records it for 6 per cent. Erucation finds frequent mention; Hirsch reports it for 5 per cent. Nausea is common; Hirsch reports it in 13 per cent.; Seeger reports frequent nausea, with vomiting or feeling of faintness in 49 per cent. Vomiting may occur, and in some instances the tapeworm or portions of it have been vomited; this is of course particularly dangerous if the worm is *Tænia solium*; Hirsch reports matitudinal vomiting in 1 per cent., frequent vomiting in 12 per cent.

Abdominal pains are very commonly complained of: they may be of the nature of colic or of gastralgia; they are referred to different parts of the abdomen, are of varying severity, sometimes intermittent; there may be borborygmi, a sense of distortion or twisting in the bowels, or a sensation of a ball or weight rolling around in the abdomen following the movements of the body. In experimental infection on myself the most pronounced and common symptom was that peculiar sensation one often has upon the sudden descent of an elevator; this occurred particularly while walking. Huber, in experiments upon himself, experienced a gnawing sensation in the epigastrium. The colic-like pains may increase after certain foods (herring, onion, garlic, and sour foods) or decrease after milk, eggs, and oily foods (Hemmeter, 1902). Seeger reports abdominal pains of various sorts in 42 per cent., and peculiar sensations of movements in the abdomen in 16 per cent., acute colic, 17 per cent.; Hirsch reports abdominal pains as common, colic in 14 per cent. Digestive troubles are reported by nearly all authors. Constipation (5 per cent., Hirsch), diarrhœa (6 per cent., Hirsch) or irregularity of bowels (3 per cent., Hirsch) may obtain. Seeger reports digestive troubles and irregularity of bowels in 33 per cent.

Anæmia is most likely to occur in infections with *Dibothriocephalus latus*, less likely with *Tænia saginata* and is said by some authors not to occur with *Tænia solium*. Hirsch reports anæmia in 1 per cent., chlorosis, 1 per cent., paleness, 4 per cent., icterus, 2 per cent.

Unequal pupils are very commonly recorded; disorders in vision, as narrowing of visual field, amaurosis, monocular polyopia, are on record. Ringing or humming in the ears, disturbances in hearing, and deafness are mentioned. Headache is more or less common (14 per cent., Hirsch); Seeger reports periodical and habitual headache, usually unilateral (19 per cent.) and vague pains in different parts of body (11 per cent.) Itching and dryness of the nose and epistaxis are more or less common. According to Davaine, anal pruritis, like nasal pruritis, may be attributed to a sympathetic influence but is usually due to irritation of the

¹The statistics quoted from Cobbold (1883a), Hirsch (1879), and Seeger (1852), are based upon infections with large tapeworms and to a certain extent represent selected cases. Ransom (1904) has published a very instructive compilation of the symptoms reported for 49 cases of infection with the dwarf tapeworm; the reader is referred to Ransom's paper for details since so many complex factors enter into consideration that to quote these details, not all taken from one observer, in comparison with the statistics quoted for the large tapeworms, would require a lengthy discussion extending beyond the limits prescribed for this article. In general it may be said that the same symptoms recorded for the large tapeworms may occur also in connection with the dwarf tapeworm.

lining of the lower part of the intestine produced by contact and movement of detached segments; nasal pruritis (12 per cent., Hirsch) is less frequent than anal pruritis (19 per cent., Hirsch) but it is rare (Davaine) that a patient has neither.

Emaciation is common when the infection is of long standing and may be accompanied by bloating and distension of the abdomen. There may be gradual loss of strength (4 per cent., Hirsch), a general and continued weariness (4 per cent., Hirsch), or weakness, especially in the knees (2 per cent. Hirsch); cramps and pains in the limbs may be severe enough to interfere with the usual occupation (Davaine). Disturbed sleep is common; complete insomnia or abnormal sleepiness may be present in about 1 per cent. (Hirsch); insomnia may be persistent. Vertigo, which many authors mention, Seeger records in 15 per cent., Hirsch in 16 per cent. Epileptiform attacks (*epilepsia teniosa*) are mentioned by a number of authors; the symptom is rare, 1 per cent. (Hirsch), and may occur in patients as young as three years (Comby); the attacks do not attain the severity of true epilepsy; the aura is of long duration, the convulsions may last ten to fifteen minutes and the stage of coma is equally long; all stages are more prolonged than in ordinary epilepsy (Comby) and there is a tendency to periodicity (Martha, 1892).

Among other symptoms reported are: chorea, 2.3 per cent. (Cobbold); severe manifestations of convulsive nature, 2 per cent. (Hirsch); convulsive fits (Cobbold, 1 in 130); loss of memory; momentary loss of speech; failure and derangement of speech, 1 per cent. (Seeger) and of special senses, 15 per cent. (Seeger); cough; weakening of mental faculties; loss of consciousness, 2 per cent. (Hirsch); hysteria; paralysis; tremors; pyrosis, 8 per cent. (Hirsch); cardiac palpitation, 6 per cent. (Hirsch); urticaria chronica (Heffter, 1855a); herpes (Bigelow, 1848a); pleuritis-like conditions (Beauchamp, 1876a); etc.

Treatment.¹—In considering the advisability and the time of treatment emphasis may again be laid upon the point that if *Tænia solium* is present, especially in patients with a tendency to vomit, no unnecessary time should be lost in expelling the worm; in case of infection with any of the other species mentioned, prompt treatment is advisable on general principles but a postponement for a few days or even a few weeks or months to suit the convenience of the patient or physician, is of less serious moment. During such period, however, the patient should have a care not to defecate in any place where the eggs in his discharge can gain access to the intermediate host.

Special precautions are to be taken, or the treatment is to be indefinitely postponed, according to circumstances, in cases of pregnancy, or in patients especially debilitated from other cause than tænia, and in convalescence, tuberculosis, and cancer.

Having decided upon treatment, three points in particular are to be held in mind: (1) the clearer the bowels are the better the chances for expelling the parasites; (2) the older the drugs the less are the chances for success; (3) the tapeworm is an animal with a highly organized nervous system. Corresponding to these important facts, there are three periods in treatment:

¹ See also remarks under the various species discussed.

1. Preparatory Treatment.—Place the patient on a light diet for two or three days, avoiding bread and vegetables and such food as is likely to increase the faecal material; allow chiefly liquid diet, milk, broths, eggs, etc. Many physicians prefer, not without good reason, to withhold food absolutely for twenty-four hours immediately preceding the administration of the anthelmintic. At the same time give a mild laxative, such as a few doses of sulphate of soda, or a teaspoonful of compound licorice powder in water in the mornings, and take every precaution to empty the bowels thoroughly, as by a saline purgative the night before the anthelmintic treatment, and enemata the night before and the morning of treatment. The object of this is twofold: the smaller amount of contents in the small intestines the less the tapeworm is protected from the drug; and if the worm meets with an obstruction as it descends, it may have a chance to recover its hold and thus remain in the intestines. Some authors advise a salad of dried herring, garlic, and onions the night before treatment.

2. Anthelmintic Period.—Early in the morning, following the period of preparation, coffee may be allowed but no solid food. Then take any one of the standard *tæniifuges*, provided it is fresh. For the comfort of the patient it is well for him to remain in bed or on a couch during this period, as various disagreeable symptoms (syncope, vertigo, vomiting) may otherwise arise.

Of the numerous tapeworm remedies, certain are recognized as more or less standard but it would be difficult to obtain a great majority vote for any one of them to the exclusion of the others. The following are among those which are most popular:

Male fern:¹ This is perhaps the most commonly used drug in this country and parts of Europe for the expulsion of *Tænia* and *Dibothriocephalus*. In Europe larger doses are administered than in America. Its oleoresin or ethereal extract is usually given and should be fresh. The dose is 2 to 8 grams ($\frac{1}{2}$ to 2 drams) either in a simple syrup or in gram gelatine capsules, which may be coated with keratin in order to prevent their solution in the stomach and thus have the drug reach the worm in more concentrated form; the capsules are taken at intervals of about fifteen minutes. In an overdose, male fern is a distinct poison and it is reported that 24 grams (6 drams) have caused death. Some authors advise that the dose should never exceed 10 grams ($2\frac{1}{2}$ drams), while others maintain that doses higher than 8 grams (2 drams) are both unnecessary and not devoid of danger. Authors also advise against its administration two days in succession and on an absolutely empty stomach. Some authors advise its administration in pills. The last dose should be followed in thirty to sixty minutes by a full dose of salts (as magnesium sulphate) or calomel and salts, rather than with oil which increases its absorption.

Cusso (or Kosso, or Koussou).—This drug is used most frequently in certain parts of Africa and is highly recommended by several prominent authors. It must be quite fresh. Heller prefers it, and Tyson (1903)

¹For the properties and characteristics of this and other drugs mentioned, the reader is referred to the pharmacopœia and works on therapeutics and materia medica, as a detailed discussion of these points cannot be given in this short article.

says that in his hands *cusso* "has been decidedly the most efficient" remedy. It should never be given in case of pregnancy. Dose 20¹ grams (5 drams) for *Tænia solium*, 30 grams (7.5 drams) for *T. saginata*. There are several "best" methods of administering it. One is to make an infusion in 240 Cc (8 ounces) of water; a more pleasant method is to give 5 grams (75 grains) in a glass of white wine every half hour until four doses are taken; or it may be mixed with honey, enclosed in capsules, compressed into tablets, or combined with male fern.

Generally this requires no purgative but if no movement of the bowels has taken place after six hours, castor oil, compound jalap powder, or elaterium is given.

Kamala.—*Kamala* is administered in doses of 4 to 8 grams (1 to 2 drams), in syrup or cinnamon water, sweetened coffee or tea, or the fluid extract (2 to 4 Cc.— $\frac{1}{2}$ to 1 dram) is given. It is a purgative and may cause nausea, vomiting, and griping.

Bark of Fresh Pomegranate Root.—This is given third place by Tyson. Hemmeter advises 50 grams (1 $\frac{3}{4}$ ounces), macerated for twenty-four hours in 500 Cc. (16 ounces) of water; then evaporate down to 250 Cc. (8 ounces) and add syrup of orange peel, 30 grams (1 ounce); to be taken in two parts. It often causes nausea, giddiness or faintness. The fluid extract, 2 to 8 Cc. ($\frac{1}{2}$ to 2 drams) is a more convenient dose.

Pelletierine, an alkaloid prepared from pomegranate, is especially popular in France. It is given in doses of 0.3 to 1.3 grams (5 to 20 grains). Tanret's preparation is the most popular but none except fresh importations should be used. The efficacy of the tannate is said to be increased and its toxic action diminished by preceding it with a few grains of tannic acid.

Pomegranate preparations should be followed within an hour by a brisk cathartic. Some authors give half an ounce of magnesium sulphate twenty minutes before and the same dose twenty minutes after the pelletierine.

Decorticated Pumpkin Seed.—This is an old and rather popular remedy, which has been known to expel *Tænia saginata* when the foregoing drugs have repeatedly failed; it is the safest and a good drug for children. Tyson, however, places it below the foregoing in efficiency. It is given in various ways:

(a) 30 to 120 grams (1 to 4 ounces) of the seed are crushed and given in a strained emulsion followed by a brisk purgative.

(b) The seeds are made into an electuary, "which is almost as pleasant as sugar candy, and often about as effectual" (Tyson, 1903).

(c) Seeds are carried in the pocket and eaten at short intervals for two or three days till the worm passes.

Some authors advise that pumpkin seed be preceded by castor oil or by effervescent magnesium citrate, this to be repeated two hours after the anthelmintic if the tapeworm has not been expelled.

Santonin is advised by some authors, but the writer, in experiments upon himself (with *Tænia saginata*) found it useless. *Thymol* has been recommended by various authors, but in laboratory experiments

¹Some authors advise only one-fourth to one-half this amount, but writers who are high in the praise of *cusso* give large doses.

upon dogs, the writer has failed to obtain positive results (infection with *Dipylidium caninum*). Naphthalin has its admirers (dose 0.1 to 0.6 gram—2 to 10 grains—followed in an hour by a cathartic). *Cocoanut* has been gaining in repute; the entire milk and meat of one cocoanut is taken, followed by a purge.

Chloroform, oil of turpentine (with equal or twice the quantity of castor oil), zinc filings in syrup, oil of pine needles, and various other drugs have their advocates. As one of the curiosities in helminthology, mention may be made of the existence of a patent tapeworm trap which the patient is directed to swallow; the tapeworm is supposed to put its head into the trap which is then induced to pass from the bowels!

3. Expulsion.—The patient should be instructed to use a vessel containing warm water while passing the worm and under no circumstances to pass it into a water closet, a privy, or a cold chamber. If the worm comes in contact with a cold object, while a portion of its body is still in the warm intestines, it may contract so suddenly and violently as to break; the head may thus remain in the bowels. The patient should be further instructed not to pull on the worm, should this be coming slowly, but rather to use injections of warm water. If the physician is present during the passage of the worm, the *parasite* is sometimes given an injection of morphine. Finally the patient should submit the entire stool to the physician for examination. Search is made for the head, to determine whether the treatment has been entirely successful. Should the head not be found, it is still possible that it has been passed, so that it is unnecessary to repeat treatment until (after several months) segments or eggs again appear in the stools.

Treatment of Children.—The treatment of children is of course attended with greater difficulty than the treatment of adults. Comby advises cusso 10 grams (2.5 drams), or decoction of fresh pomegranate bark, 15 to 20 grams (4 to 5 drams), or ethereal extract of male fern, 4 to 6 grams (1 to 1.5 drams), or pumpkin seed in emulsion 50 to 60 grams (1.66 to 2 ounces). Comby gives ethereal extract of male fern, 4 grams (1 dram)+essence of turpentine 1 gram (15 minims)+syrup of orange flower 30 grams (1 ounce)+peppermint water 70 Cc. (2.33 ounces); taken at one dose by child five to ten years old and followed in half an hour by 15 to 20 grams (4 to 5 drams) of castor oil (see, however, p. 562). French prefers, for children, drugs in the following order: pumpkin seed mush, cocoanut, black oxide of copper, pelletierine.

SOMATIC TÆNIASIS.

Somatic tæniasis, due to infection with the larval stage of tapeworms, may be of three kinds (in order of their importance): hydatid disease, due to infection with the larval *Echinococcus granulosus*; cysticercosis, due to infection with the larval *Tænia solium*, known as *Cysticercus cellulosæ*; and infection with bothriocephalid larvæ, classified as *Sparganum mansonii* and *S. proliferum*.

Cysticercosis or Infection with Larval Tænia Solium—Geographical and Zoölogical Distribution.—See p. 561.

The Larval Parasite.—In the early days of helminthology, what we now know to be the larval stage of *Tænia solium* was supposed to represent a distinct species of animal, to which the name *Cysticercus cellulosæ* was given. This larva is an elliptical, translucent, bladder-like structure, 6 to 12 mm. long by 5 to 10 mm. broad, with a white spot at its equator, due to the invaginated head. While it usually agrees with the same organism as found in hogs, it may (particularly when located in the subarachnoidal spaces) grow to a larger size and assume an irregularly branched form, described as *Cysticercus racemosus*. The parasite inhabits the subcutaneous connective tissue, muscles, brain, spinal canal, eye, heart, lymphatic glands, tongue, liver, bones, lungs, kidney, mammary gland, or prepuce, producing symptoms which vary according to the location and number of parasites present. In some cases, especially in very light infections, no symptoms may be observed and the infection is discovered at autopsy. In other instances, particularly in case of location in the brain or eye, the infection is of more importance and in case of cerebral infection it may result fatally. If the parasite is in the eye, it is more likely to be discovered by the ophthalmologist than by the practicing physician, so that in an article of this kind reference to the infection will suffice. In case of cerebral infection the symptoms are varied according to the exact location; in case of continued pain in the head, visual disorders, mental disorders, with depression and confusion or dizziness, unilateral paralysis, epileptiform, subacute, cumulative spasms, especially in patients over forty years of age, and showing concurrent adult *Tænia solium* in the intestine, or recent history of such intestinal infection, the possibility or even probability of infection with the larval stage should be borne in mind.

It takes about three months for the parasite to develop from the six-hooked embryo (onchosphere) to the bladderworm stage, which may live in man as long as twenty years. A patient may harbor from one to several thousand bladderworms, the heavy infections probably representing cases in which an entire segment of the tapeworm has gained access to the stomach through the pylorus.

There is no medical treatment; Feletti (1894a,) however, claims good results with male fern, 1 to 3 grams (15 to 45 grains) for several days. Surgical interference may be resorted to if the parasite can be located. A number of cases of extractions of bladderworms from the eye are recorded.

Cysticercosis is decreasing hand in hand with the decrease of the adult worm; the latter is decreasing as a result of meat inspection and better curing and cooking of pork.

Cysticercus bovis, the larval stage of *T. saginata*, is alleged to have occurred in man, but as *C. cellulosæ* may lose its hooks and thus resemble the larval stage of *T. saginata*, doubts arise regarding the correctness of the determinations.

Cysticercus acanthotriax Weinland, 1858, characterized by the presence of three rows of hooks on the head, and taken as the type of a special genus *Acanthotriax*, is now interpreted as simply an anomaly of *C. cellulosæ*.

Tænia hydatigena (Batsch, 1786), is a tapeworm very closely allied to *Tænia solium*, with which it was for years confused. The mature worm lives in dogs; the larval stage, known as *Cysticercus tenuicollis*, is found

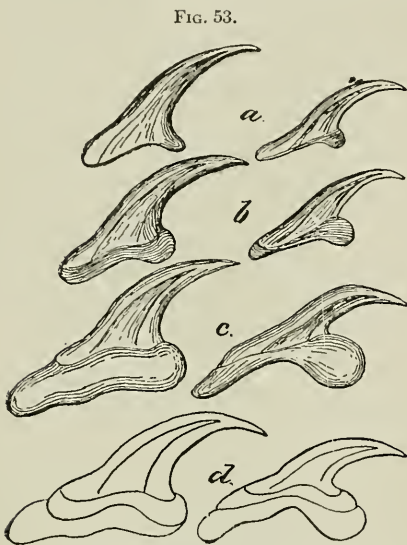
in cattle, sheep, hogs, etc., and is reported for certain monkeys; the cysticercus has also been reported for man but the correctness of the zoological determination has been called into question.

Echinococcosis: Echinococcus Disease; Hydatid Disease.—**Geographical Distribution.**—This infection is practically cosmopolitan, but is found especially in Iceland, certain parts of Germany, and in Australia. Many of the cases reported for the United States have occurred in immigrants who were doubtless infected before they came here, but we also have the parasite as part of our American fauna.

Zoological Distribution.—The adult tapeworm occurs in the upper half of the small intestine, but never close to the stomach, of dogs, wolves, jackals, *Canis dingo*, and it can develop in cats. The larval stage occurs in quite a number of domesticated animals, as sheep, cattle, hogs, and

also in certain wild animals, being reported in all from twenty-seven species of mammals. From the public health point of view it is especially the dog, sheep, cattle, and swine which come into consideration. Man is probably an accidental though not a rare host.

The Parasite.—It is at present an open question upon which there may be a legitimate difference of opinion, whether one, two, or three distinct species or varieties of echinococcus should be recognized. Most zoologists admit only one species, commonly known as *Tænia echinococcus* (Zeder, 1803) Siebold, 1853, but the writer agrees with Weinland that it is well to place this in a distinct genus; if this is done the correct name of the species is *Echinococcus granulosus*¹ (Batsch, 1786) Zeder, 1803.



Hooks of hydatid tapeworm: *a*, from a hydatid; *b*, three weeks after feeding to a dog; *c*, from an adult; *d*, combined figures of *a-c*, showing the gradual changes in form. $\times 600$. (Leuckart.)

This is one of the smallest tapeworms known. It is composed of a head with 28 to 50 hooks, a short neck, and 3 or 4 segments; the first segment is immature, the second is mature, the last segment is gravid and it composes about $\frac{1}{2}$ (2. mm.) of the total length (2.5 to 5 mm.) of the worm. The larval stage of this worm is the largest larval cestode known, and is the *Echinococcus*² or *Echinococcus hydatid* of medical and zoological authors.

¹GENERIC SYNONYMS.—*Echinococcus Rudolphi*, 1802; *Acephalocystis Lænnec*, 1804.

SPECIFIC SYNONYMS.—Adult: *Tænia nana* van Beneden, 1861, (not Siebold, 1853); *Tænia echinococcus* (Zeder, 1803) Siebold, 1853; *Echinococifer echinococcus* (Zeder) Weinland, 1861.

²*E. polymorphus* Diesing, 1850; *E. unilocularis* Huber, 1896; *E. cysticus* Huber, 1891.

This may assume a number of different variations in growth, as will be described below.

One of the peculiar extreme forms, the multilocular echinococcus, is recognized by some authors as a distinct parasite but most writers deny

FIG. 54.

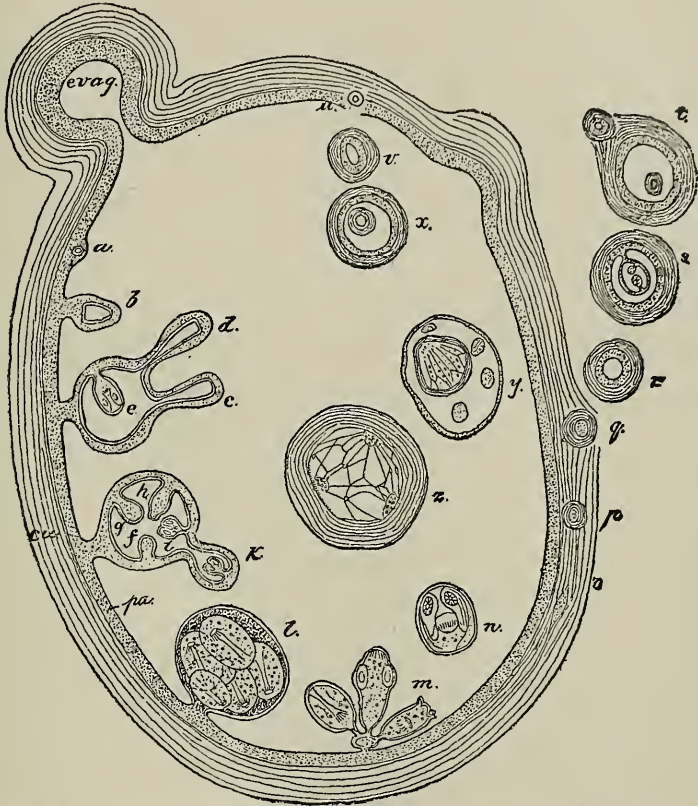


Diagram of an *Echinococcus* hydatid: *cu*, thick external cuticle; *pa*, parenchym (germinal) layer; *c, d, e*, development of the heads according to Leuckart; *f, g, h, i, k*, development of the heads according to Moniez; *l*, fully developed brood capsule with heads; *m*, the brood capsule has ruptured, and the heads hang in the lumen of the hydatid; *n*, liberated head floating in the hydatid; *o, p, q, r, s*, mode of formation of secondary exogenous daughter-cyst; *t*, daughter-cyst, with one endogenous and one exogenous granddaughter-cyst *u, v*, formation of exogenous cyst, after Kuhn and Davaine; *y, z*, formation of endogenous daughter-cysts, after Naunyn and Leuckart; *y*, at the expense of a head; *z*, from a brood capsule: *evag.*, constricted portion of the mother-cyst. (R. Blanchard slightly modified.)

its right to distinct rank. It would seem to the writer that the present evidence, based largely upon geographical distribution and the larva, more than the adult stage, entitles it to rank as a sub-species, possibly as a species. If recognized as of sub-specific rank the correct name is *Echinococcus granulosis multilocularis*;¹ if recognized as a distinct species the correct name is

¹SYNONYMS.—*Echinococcus multilocularis*; *E. alveolaris*; *E. multilocularis exulcerans* Huber, 1896; *E. osteoklastes* Huber, 1896.

Echinococcus multilocularis. The finer points of distinction between the adult of this form and the typical form call for further investigation; the larval form or multilocular echinococcus is the "Gallertkrebs," "alveolar colloid," or "colloid cancer," usually found in the liver and reported, in man, especially for Russia, Bavaria, Switzerland, Württemberg, Austria, the Alps, and Baden.

Von Ledenfeld (1886) states that an echinococcus tapeworm occurs in the dingo in Australia and may attain 10 to 30 mm. in length. The writer has not examined these worms, but unless confusion has here occurred with some other species, he would incline to the view that this parasite represented a distinct species.

Life-Cycle of the Parasite and Source of Infection.—The gravid, terminal segment of the tapeworm is discharged in the feces of the dog, and the egg, which is said not to be very resistant, gains access to the intermediate host (sheep, cattle, hogs, man, etc.) through contaminated food or drinking water, or in the case of man, possibly also from hands soiled while petting dogs. Upon arriving in the stomach, the oncosphere (six-hooked embryo) escapes from the shell and, by means of its hooks, bores its way to various parts of the body, especially to the liver. Here it comes to rest and increasing gradually in size it presents a thick outer cuticle and an inner parenchymatic layer surrounding a cavity containing fluid. An outer connective-tissue cyst is furnished by the host. This simple form is known as an *Acephalocystis* Lænnec, 1804. Brood capsules arise from the parenchymatic layer and hang into the cavity; heads form in these brood capsules. If this stage is fed to dogs each head develops into a tapeworm. The growth of the hydatid need not stop at the stage last mentioned but daughter-cysts and even granddaughter-cysts may form and fall into the cavity of the mother-cyst; this variation represents the endogenous echinococcus,¹ and is the more common variation as it occurs in man; it may attain 10 to 15 kilograms (22 to 33 pounds) in weight; the daughter-cysts may be numerous, "twenty-five to fifty" or up to "thousands." In still other cases the daughter-cysts pass outside of the mother-cyst into the surrounding tissue, thus giving rise to the exogenous echinococcus,² a rather infrequent variation in man, but more common in ruminants, pigs and the horse. It occurs in the omentum, peritoneum, kidneys, mammary gland, and brain, exceptionally in the liver, but it never attains the enormous size sometimes seen in the endogenous variation.

Frequency.—We are hardly able at present to give even approximate statistics covering the frequency of echinococcus infection in the United States. The writer recalls one abattoir (in Kansas City), where this infection in hogs was estimated several years ago at 1 per cent. This would indicate that in certain rural localities, indigenous cases have probably occurred in man which have escaped attention. Several years ago a former assistant (H. O. Somer) of the writer collated 100 cases in man for the United States and 12 cases for Canada, but as 33 of the United States cases were reported for New York alone, these statistics

¹*E. altricipariens* Küchenmeister, 1855; *E. hominis* (Zeder, 1800) Rudolphi, 1810. *Echinococcus endogena* (Kuhn, 1830); *E. hydatidosus* Leuckart, 1863.

²*Echinococcus granulosis* (Batsch, 1786) Rudolphi, 1805; *E. veterinorum* Rudolphi, 1810; *E. exogena* (Kuhn, 1830); *E. scolecipariens* Küchenmeister, 1855.

must surely cover only a percentage of the cases which have actually occurred; they further show quite a percentage as having been found in foreigners, and as probably many, if not most of these latter brought their infection with them to this country, the figures can hardly be taken as representing American conditions. We may expect more cases in rural and village districts in which the "country slaughterhouse" flourishes. In Manitoba, the infection has been common among the Icelanders. Of the English-speaking countries, Australia has presented the highest figures; the province of Victoria, for instance, is said to have 3 per 1,000 mortality from hydatids and 1 case of echinococcus for every 175 hospital patients, while 1.61 to 2.73 per cent. mortality is said to occur in South Australia. The estimate of 400 deaths per year for England is very difficult to accept, especially in view of the comparatively few articles on this disease in the current English medical journals, but Huber quotes Murchison as reporting about 1.5 per cent. infection in his postmortem examinations. In certain parts of Continental Europe, echinococcus disease is not uncommon; thus Madelung reports for Rostock 1 case per 1,056 inhabitants; from 1861 to 1883, Rostock also showed 25 post-mortem cases in 1,026 autopsies, or 2.43 per cent.; and the slaughterhouse statistics for entire Germany give an average of 10.39 per cent. for cattle, 9.83 per cent. for sheep, and 6.47 per cent. for hogs.

Iceland is recognized as the classical echinococcus land, but some of the estimates published must be taken with reserve. The more conservative statistics give the infection as from 1 in 43 to 1 in 63 of the inhabitants and Krabbe reports it for 25 per cent. of the dogs.

Hydatids seem to be more common in females than in males, but some statistics give them as more common in males, and according to Meisser, they occur more commonly in patients from twenty-one to thirty years of age (about 30.8 per cent. of the cases collected), than from thirty-one to forty years (about 24.6 per cent.), forty-one to fifty years (about 15.2 per cent.), eleven to twenty years (about 13.2 per cent.), fifty-one to sixty years (6.2 per cent.), 0 to ten years (4.8 per cent.), sixty-one to seventy years (2.8 per cent.), and seventy-one to eighty years (1.4 per cent.).

The parasite is most commonly located in the liver. Thus, of 1,806 organ-infections, the following organs were the most frequently affected: liver (1,011), lung (147) and kidney (126); the parasite can, however, develop in any portion of the body.

Duration.—The growth of the echinococcus is very slow; according to Leuckart's experiments on swine, it takes five months for the cyst to reach a diameter of 15 to 20 mm. If scolices are fed to dogs, the development of the adult worm is also slow; about ten to twelve weeks may be required for the worm to reach the gravid stage.

How long an hydatid cyst might live in man is an open question; it has been stated that 50 per cent. of the infections are fatal within five years, but as many cases are doubtless not diagnosed, statistics on this point are naturally always open to some question. Authority exists for cases in man of two to eight years duration and even longer.

Symptoms.—The symptoms of echinococcus disease are practically those of a slowly growing tumor, which may attain 10 to 20 kilograms (22 to 44 pounds) in weight and which causes different symptoms according to its location. In some cases the worm may die, the parasite

then collapses and the cyst becomes gelatinous and thick; the heads, or at least the hooks, may be found in the altered, thick, opaque contents. In some cases the cyst may suppurate. The hydatids are occasionally discharged through various channels (bile-ducts, lungs, in urine, etc.). Urticaria may develop upon the rupture or puncture of the cyst admitting the echinococcus fluid into the body cavity, but it is said to occur also in case of apparently uninjured cysts.

Diagnosis.—In many, but not all cases, the so-called hydatid thrill or fremitus is felt on percussion, resembling the quivering of jelly. Deeply seated echinococci give an elastic feeling, superficial parasites a fluctuation. Positive diagnosis may be made microscopically by finding the hooks or heads in case of discharge, or in the aspirated fluid; and presumptive diagnosis may be made by finding sugar in the aspirated fluid. The multilocular echinococcus is usually in the liver and accompanied by a chronic icterus.

Treatment.—Numerous methods of medicinal treatment have been proposed for hydatid disease, all having one attribute in common, namely, apparent uselessness. Echinococcus infection is a surgical disease and in our present knowledge of the malady only surgical interference is capable of curing it. For the technique of operation, the reader is referred to works on surgery. Several authors refer to "boldly incising the cyst," but attention may be directed to the fact that by opening the external cyst (namely the surrounding cyst which is furnished by the host) very cautiously, the inner cyst (namely the parasite itself) can be taken out entire; to do this the external cyst should be raised at a convenient point leaving a small space between it and the inner cyst. To gain experience in this operation it is well to practice on several echinococcus livers of hogs or other animals from a slaughter house; judging from the observations of the writer on the killing floors of our large abattoirs, such experimental material is not difficult to obtain. Strictly aseptic tapping has been followed by recovery. In the event of suppuration the condition is treated as one of abscess.

Prevention.—Since this disease is transmitted from dogs to man, and since dogs obtain their infection more particularly from eating the infected organs of slaughtered sheep, cattle, and hogs, it is clear that any plan of prevention should follow two lines: *First* and most important, dogs should be kept away from slaughter houses in order to prevent them from eating the organs rejected on account of hydatid infection; the rule that no dog which enters a slaughter house or its refuse yard should ever be allowed to leave would, if carried out, save many lives and much valuable live stock, but it is difficult of practical application. *Secondly*, whatever our affection may be for "Old Dog Tray," we should recall that he is a dog and not a human being; in his place he is useful, but out of his place he may be a very dangerous friend.

So far as can be judged from the federal meat inspection, hydatid disease is much more common than is generally supposed. As stated above, the writer recalls one abattoir where the infection among the hogs was estimated at 1 per cent.; with this percentage it seems positive that in some sections of the country the parasite has developed to such an extent that local boards of health should institute measures for its control by placing the local slaughter houses under sanitary supervision.

Sparganum Mansoni (Cobbold, 1882) is a larval bothriocephalide tapeworm reported 10 times¹ in the Japanese. It measures 8 to 36 cm. in length by 0.1 to 12 mm. in breadth, and 0.5 to 1.75 mm. in thickness; it is flat and unsegmented and as yet no stage with genital organs has been found. It occurs in the subperitoneal connective tissue and body cavity of man in Amoy and Japan. Sonsino reports it for the jackal in Egypt. Daniels found this or a similar parasite in British Guiana. Of the Japanese cases, 7 of the patients were males, 2 were females, 1 unstated. By age: 1 case occurred in a patient nine years old, 3 cases between eleven and twenty, 3 between twenty-one and thirty, 1 between thirty-one and forty, 1 between forty-one and fifty, 1 unstated.

The parasite was lodged in the region of the eye in 3 cases; it escaped from the urethra in 4 cases; was in the connective tissue of abdominal region in 1 case and in the pleural cavity in 1 case. A single parasite was reported in 9 cases, 12 parasites in 1 case.

Looss (1905) suggests that the escape of the worm through the urethra indicates that the definite host is an aquatic animal and he thinks the regular intermediate host may possibly be one of the large ruminants.

Surgical treatment should be used in superficial swellings, while in urethral cases the worm should be extracted while the patient is in a warm bath, the parasite being slowly drawn out or wound around a stick under water. It might perhaps be well to give the parasite a hypodermic injection of morphine shortly before pulling it out.

Sparganum proliferum² (Ijima, 1905) is a peculiar larval Japanese cestode reported but once. It occurred in the subcutaneous tissue, especially of the leg, and produced acne-like swelling and a condition somewhat similar to elephantiasis. The worms measure 1 to 12 mm. long by 2.5 mm. in breadth, and possess the peculiarity of reproducing by budding. Adults and life history are unknown.

¹For compilation of cases to date, see Stiles and Tayler, 1902, pp. 47-56, figs. 30-36.

²SYNONYMS.—*Plerocercoides prolifer* Ijima, 1905; *Plerocercus prolifer* Ijima, 1905.

CHAPTER XXVI.

ROUNDWORM INFECTION—NEMATHELMINTHES.

By CHARLES WARDELL STILES, PH. D. D.Sc.

THE roundworms are divided into three orders (see key, p. 531), namely the *Nematoda*, the *Gordiacca* and the *Acanthoccephali*. Of these, the nematodes are by far the most important, while the horse-hair worms and the thorn-headed worms are of secondary importance in human medicine. For practical reasons they will be arranged in this article according to the part of the body they inhabit instead of according to their zoölogical arrangement. Systematically the nematodes parasitic in man are classified as follows:

- Family Anguillulidæ: genera *Anguillula*, p. 624; *Anguillulina*, p. 602;
Leptodera, p. 624; *Rhabditis*, p. 611.
- “ Angiostomidæ: genus *Strongyloides*, p. 595.
- “ Gnathostomidæ: genus *Gnathostoma*, p. 611.
- “ Filariidæ: genera *Filaria*, p. 613; *Dracunculus*, p. 611;
Agamofilaria, p. 623.
- “ Trichinellidæ: genera *Trichinella*, p. 605; *Trichuris*, p. 603.
- “ Strongylidæ: genera *Metastrongylus*, p. 610; *Trichostrongylus*, p. 602;
Uncinaria, p. 583; *Agchylostoma*, p. 584;
Necator, p. 583; *Diectophyme*, p. 624;
Physaloptera, p. 602.
- “ Ascaridæ: genera *Ascaris*, p. 597; *Toxocara*, p. 597; *Oxyuris*, p. 600.

INTESTINAL ROUNDWORMS.

Uncinariasis¹ or Hookworm Disease.—Geographical Distribution.—Uncinariasis encircles the globe in the tropical and subtropical belt, diminishing in frequency in the temperate climates, but occurring locally in mines as far north as England, Holland, and Germany in Europe; in North America the endemic infection stops about at the Potomac River.

Zoölogical Distribution.—Generically identical, but specifically distinct infections occur in dogs, cats, foxes, and various other animals. The infection of cats, which was supposed to be specifically identical with the Old World hookworm of man, has proved to be distinct and the infection of the chimpanzee, supposed to be identical with the New World hookworm of man, is also probably distinct.

¹SYNONYMS.—Anchylostomiasis; ankylostomiasis; brick-makers' anæmia; dirt eating (in part); doehmiosis; Egyptian chlorosis; geophagia (in part); malarial anæmia (in part); malnutrition (in part); miners' anæmia; miners' cachexia; negro consumption; St. Gothard tunnel disease; tropical chlorosis; tunnel anæmia; tunnel disease.

The Parasites.—Hookworm disease in man is known to be due to two distinct species of parasites belonging to the subfamily Uncinariinae,¹ namely, the Old World hookworm and the New World hookworm.

The New World hookworm, *Necator americanus*² (Stiles, 1902) or

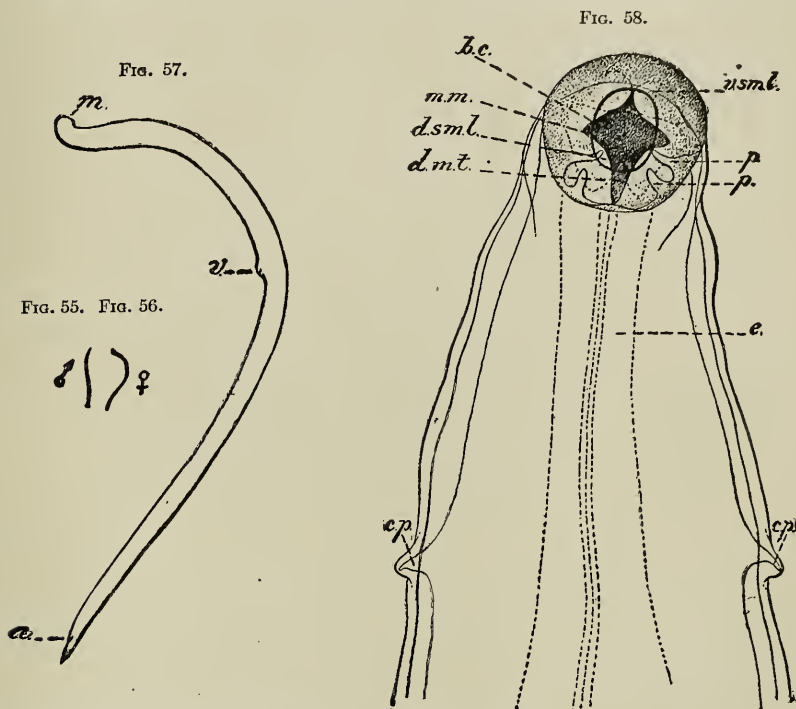


FIG. 55.—New World male hookworm. Natural size. (Stiles.)

FIG. 56.—New World female hookworm. Natural size. (Stiles.)

FIG. 57.—The same, enlarged to show the position of the anus (a) and the vulva (v). (Stiles.)

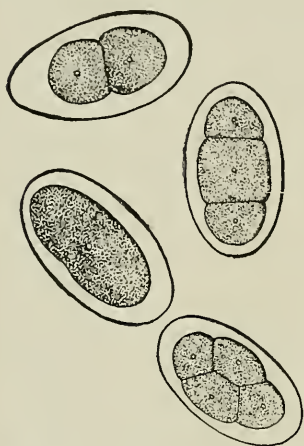
FIG. 58.—Dorsal view of anterior end of New World hookworm: b. c., buccal cavity; c. p., cervical papillae; d. m. t., dorsal median tooth, projecting prominently into the buccal cavity; d. sm. l., small dorsal semilunar lip; c., oesophagus; m. m. margin of mouth, the prominent oval opening seen upon high focus; p. p. papillae; v. sm. l., large ventral semilunar lips homologous with the ventral hooks of *A. duodenale*. Greatly enlarged. (Stiles.)

¹ As this group of worms is more carefully studied, it becomes apparent that the old genus *Uncinaria* (type *vulpis* = *criniformis*) must be divided into at least four smaller groups: *Uncinaria* (type *vulpis*), *Agchylostoma* (type *duodenale*), *Necator* (type *americanus*), *Bunostomum* (type *trigonocephalum*), and probably into several additional units. Opinion will probably differ for some time to come as to whether these units represent genera or subgenera, but evidence is accumulating to the effect that they should be given generic rank. Changes in the generic nomenclature in consequence of such division, are of course unavoidable, in the same way that a new terminology had to be used when (1860) trichinosis was differentiated from typhoid fever. No changes, however, in the specific nomenclature of the two forms (*americanus* and *duodenale*) found in man can be foreseen.

² SYNONYMS.—*Uncinaria americana* Stiles, 1902; *Ankylostomum americanum* (Stiles) Linstow, 1903 (exclusive of form in the chimpanzee); *Uncinaria* (*Necator*) *americana* (Stiles); *Necator americanus* (Stiles); *Uncinaria hominis* Ashford, King and Gutierrez, 1904, in part.

Uncinaria americana Stiles, 1902, is the common hookworm of the American continent and adjacent islands but it has been introduced into Italy, and doubtless also into Spain. It has been reported recently also for Africa, China, and Guam. This cylindrical worm is 7 to 11 mm. long and possesses a dorsal and a ventral pair of lips at the mouth, a prominent dorsomedian buccal tooth, and four buccal lancets; in the male, the dorsal ray of the bursa divides at the base and each branch possesses two tips. In the female the vulva is in the anterior half of the body. The eggs are thin-shelled, 64 to 72 μ long by 36 to 40 μ broad; they are oval with somewhat bluntly rounded poles.

FIG. 59.



Four eggs of the New World hookworm, in the 1, 2, and 4-cell stages. The egg showing 3 cells is a lateral view of a 4-cell stage. These eggs are found in the faeces of patients and give a positive diagnosis of infection. Greatly enlarged. (Stiles.)

The Old World hookworm, *Agchylostoma duodenale*¹ Dubini, 1843, or *Uncinaria duodenalis* (Dubini, 1843) Railliet, 1885, is the common hookworm for Europe, Asia, Africa, and Australia, but it has also been introduced to some extent into the Americas. This parasite measures 8 to 18 mm. in length and possesses in its mouth 2 pairs of strong, curved, ventral teeth and 1 pair of knob-like dorsal teeth; the dorsomedian tooth of the buccal capsule is nil or practically so; a pair of ventral lancets is present in the buccal cavity. In the male, the dorsal ray of the bursa is divided two-thirds its length from the base and each branch is subdivided into three tips. In the female, the vulva is in the caudal half of the body. The eggs measure 52 to 61 μ long by 32 to 38 μ broad; they are oval with very bluntly rounded poles.

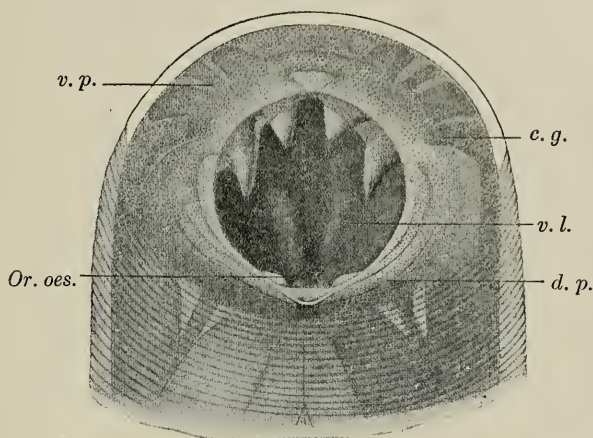
Both parasites inhabit the small intestine, especially the jejunum and ileum but also duodenum and occasionally the stomach.

Source of Infection.—The eggs are oviposited in the intestine of the patient; they do not develop until after they escape with the faeces; then they develop within twenty-four hours or more, according to conditions of heat, moisture and amount of oxygen, a rhabditiform embryo which undergoes ecdysis (shedding of skin) after about forty-eight to seventy-two hours; a second ecdysis which occurs within about five to nine days changes the worm to the infecting stage—the so-called “encysted larva”; from this point the worm takes no more food until it reaches man. Infection takes place in two different ways: (1) It has been experimentally demonstrated, first by Looss, that the hookworm larvæ may pass through the skin, reach the circulatory system, pass with the blood

¹SYNONYMS.—*Agchylostoma duodenale* Dubini, 1843; *Ancylostoma duodenale* (Dubini) Creplin, 1845; *Dochmius duodenalis* (Dubini) Leuckart, 1876; *Anchylostoma duodenale* (Dubini) Bozzolo, 1879; *Uncinaria duodenalis* (Dubini) Railliet, 1885; *Ankylostoma duodenale* (Dubini); *Ankylostomum duodenale* (Dubini); *Uncinaria hominis* Ashford, King, and Gutierrez, 1904, in part.

through the heart to the lungs, from the lungs to the air passages, up to the larynx, down the œsophagus to the stomach and then to the small intestine. Looss's theory of skin infection first met with opposition, incredulity, or reserve from various sides, but it now stands on the firm foundation of experimental proof and has been accepted not only by helminthologists who first preserved a noncommittal position toward it, but

FIG. 60.



Dorsal view of the Old World hookworm: *c. g.* opening of cephalic gland; *v. l.* ventral lancet; *d. p.* *v. p.* dorsal and ventral papillæ: note also the four teeth. Greatly enlarged. (Looss.)

also by men who at first directly opposed it. Strange and incredible as the view is, it is now not only established as a possible method of infection but evidence is rapidly accumulating to the effect that it is a common, if not the most common, method by which hookworms gain access to the system. (2) A second method of infection is through the mouth, either

FIG. 61.



Six stages in the embryonic development of Old World hookworm; *a-c.* are the stages found in fresh fæces. $\times 336$. (Looss.)

with contaminated food or water or from earth containing the hookworm larvæ and clinging to the hand. Since Looss' skin infection theory has been proved, the idea of infection through the mouth has lost many supporters, and numerous arguments are submitted to prove that it is of exceptional occurrence. That the time may perhaps come when the skin infection will be generally accepted as the most important method, may

be readily admitted, but it does not seem to the writer that the time is now here when we would be justified in looking upon infection by the mouth as a curiosity or as a method which can be practically ignored. The skin-infection, as demonstrated by Looss, is a most brilliant proof of the correctness of an old-fashioned popular view which obtained regarding infection with certain parasites, a view which was practically abandoned as being too complicated and improbable, when the mouth offered such a simple, probable, and, in some cases, demonstrated entrance for intestinal worms. And it would be wise for us now not to be carried away with these new brilliant discoveries and this demonstration of the correctness of an old-fashioned idea to such an extent that we fall into error of forgetting that worms can and do enter the system by the mouth and that, given the proper conditions, there is no reason at present evident why the hook-worm should not be taken into the body in this way.

The view advanced by several authors that the free embryos may develop into free adults, the progeny of which become parasitic, is not in harmony with what is otherwise known of this group of worms.

Frequency.—Uncinariasis is a malady the spread of which is inconsistent with a proper sewage system, cold weather or dry conditions. Accordingly, in general terms, it is more common in moist localities than in dry, more common in warm countries than in cold and more common in rural districts than in cities. Although it is one of the worst scourges of the tropics, even here its frequency may be decreased by a proper disposal of feces, for fortunately the specific infections in man are not known for other animals.

It is more common among people who come into direct contact with damp earth, as farmers, miners, tunnel-diggers and people who go barefooted, than it is among persons of other occupations and those who wear shoes.

Most authors report that it is more common among men than among women and children, but this view is not in harmony with the writer's experience, for he has found it more common and more severe in children and in women than in adult males. It is not difficult to harmonize these divergent statements. Physicians reporting for mining districts would, in general, find more cases among the miners, namely among men, for the infection here occurs chiefly "underground," while the homes in many mining districts are provided with sewage or with proper privies and the miners' families are thus more or less protected from infection. Further, most authors have reported upon cases which came to them for diagnosis and treatment, while in the investigations of the writer he went to the families in order to find the cases; hence the conditions covered by his report represent more exactly the natural conditions in the rural districts visited. Again, in rural districts containing more children and women than adult males, as found in the localities in question, under conditions favorable to infection there would naturally be more cases among the children and women; furthermore the children and women were following a life more conducive to infection, namely staying near the house, in the area of concentrated infection, more than were the men, and infection would therefore be expected to be more common among the former.

Ashford, King, and Gutierrez (1904) in their splendid "Report on Anemia in Porto Rico" found more cases (1,027 of 5,490) between the

ages of five and nine years than at any other five-year period; of the same 5,490 patients, 3,259 or 59.34 per cent. were males, and 2,231 or 40.66 per cent. were females. The percentages relative to sex will naturally vary according to customs and proportion of sexes in different countries.

In the districts which were visited by the writer, uncinariasis was pre-eminently a disease of the piney wood and sand localities, occurring less in clay regions. However this distribution was not confirmed by Ashford, King, and Gutierrez in Porto Rico. Some of the physicians in the South have confirmed the author's findings in this respect while others have obtained different results. The explanation of the different findings is not clear at present. There is evidently some factor in the case which has thus far escaped attention and which will doubtless harmonize the divergent reports. Possibly Nicholson and Rankin (1904) have given the correct clue when they state that it is not so much a question of the *sandy* nature of the soil as it is a question of *fine* soil which by its ability to hold moisture offers the most favorable conditions for development. Further, the trees would naturally protect the young worms, to some extent, against the drying effects of the sun. A certain seasonal periodicity is shown in so far that infection decreases in cold and very dry seasons, but increases in warm and moist seasons. Uncinariasis is more common and more severe among the poor than among the well-to-do, and more common among people who live under conditions of filth than among those who live under better hygienic conditions.

As for statistics, some physicians in Southern Florida estimate that 90 per cent. of the rural population in that district harbor the parasite to a greater or lesser degree, and Ashford, King, and Gutierrez estimate that about 90 per cent. of the rural population of Porto Rico are infected. In some German mines, 30 to 80 per cent. of the miners have been found infected. So far as known the infection is rare in American mines.

Symptoms.—Cases may be divided into *light*, *medium*, and *severe* infections. Under the *light* infections may be included those patients who show eggs in the faeces upon microscopic examination, but who do not exhibit any or sufficiently marked symptoms to attract special attention. These cases are numerous and are important in that they are capable of keeping a region infected and thus giving rise to severe cases; hence from a prophylactic standpoint, they should always be treated when found. Under *medium* cases may be included those persons who show a definite anæmia, while other symptoms, mentioned below, develop to an extent which attract sufficient attention to bring the patient under medical treatment; a physician in the infected district should immediately suspect uncinariasis, but the Northern physician might not be so promptly led to this diagnosis. Under *severe* cases may be classified the typical dirt-eaters who present a clinical picture which even the laity in the South recognize on sight. A fourth class, *very severe* cases, may be recognized if desired, to include those patients in whom death may occur at any moment.

It is needless to say that these four phases grade imperceptibly from the lightest to the most severe. The division suggested is a compromise between the classification proposed by the writer in 1902 and that used by Ashford, King, and Gutierrez (1904) and is here adopted from a practical standpoint in prophylaxis in order to lay stress upon that large number

of cases in which eggs may be present but no special symptoms noticed; these cases must be constantly kept in mind in any scheme for eradication of the disease, and are likely to be overlooked or ignored unless special attention is directed to them. Thus, of 16 medical students examined by the writer in one of the Southern medical colleges, 4 showed infection but only 1 of these exhibited even slight symptoms; and Nicholson and Rankin (1904) have recently shown that there are numerous cases of infection in North Carolina which were not even suspected until the microscopic examination was made. If these light cases were submitted to physical examination for enlistment in the army or navy, probably most of the men would be accepted as sound, unless some other defect were found.

General Development.—If infection occurs before puberty it is likely to retard development both physical and mental. A boy or girl of twelve to fourteen years may appear to be eight to ten and one of eighteen to twenty-two may not appear to be over twelve to sixteen.

Skin.—The skin may be waxy white to dirty yellow, tallow or tan, the color being a general superficial, but not in all cases exact, indication of the degree of anemia. It becomes dry and parchment-like, perspiration being more or less completely suppressed. Petechiæ may be observed in older cases. Pruritis may be noticed more or less frequently. Atrophy of the skin is seen in chronic cases.

Ground Itch.—As Bently (1902a) pointed out, it is very common to find a history of ground itch in hookworm districts. Of 4,741 Porto Rican patients questioned by Ashford, King, and Gutierrez on this point, 4,654 or over 98 per cent. gave a history of "mazamorro," as the dermatitis is called by the natives. "New Sump bunches" is the corresponding condition in the Cornwall miners as reported by Boycott and Haldane. Claude Smith and other observers in our Southern States report a similar condition as common. The present evidence is that this rapidly developing condition (characterized by a few itching papules to a severe dermatitis, found more particularly in bare-footed people, between the toes especially and on the sides and top of the foot, and in some cases on the buttocks or other portions of the body) is the initial symptom of uncinariasis, due to the penetration of the larvæ into the skin, and doubtless accompanied in many cases with some bacterial infection. The writer is not aware that any dermatologist has as yet made any special study of ground itch and until this is done it will be wise to leave the question open as to whether *all* cases of this affection are due to uncinariasis, especially since *Strongyloides* larvæ, also, may enter the skin. Sufficient evidence has however been presented by the supporters of the ground itch theory to compel its recognition as a very general symptom of hookworm disease.

Hair.—While the hair on the head may be normally developed, there may be a marked scarcity or absence of hair on the pubes, in the armpits, and on other parts of the body, in patients who become infected before puberty.

Edema.—Edema of the face, feet, ankles, leg, scrotum, or entire body may be present. According to the Porto Rican (1904) statistics it was most frequently found in patients showing a hæmoglobin of 20 to 49 per cent.

Wounds and Ulcers.—In a number of cases, it is noticed that even slight lesions of the skin heal slowly.

Head.—The face may show an anxious, stupid expression. The conjunctivæ may be chalky-white. The pupils have a decided tendency to dilatation; the patient may show a blank stare; night-blindness is reported in a number of cases. The visible mucous membranes vary from a natural color to a white, corresponding more or less to the degree of anæmia. The tongue may show two purplish smears, one on each side of the median lines; pigmented spots and a partial denudation of the epithelium may be observed.

Neck.—Cervical pulsation, especially in severe cases, is very evident, often being visible from six to twelve feet from the patient.

Thorax.—In emaciated cases the ribs are of course very prominent.

Abdomen.—A more or less prominent abdomen is rather common, known among the laity as “pot-belly,” “butter-milk belly” or “shad-belly,” and ascites may develop.

Digestive System.—Appetite: This may be light to ravenous; in late stages there may be complete anorexia. There is further a marked tendency to the development of abnormal appetite for sour articles as lemons or pickles, or for salt, coffee, and buttermilk, or a perverted appetite for resin, charcoal, chalk, tobacco ashes, dried mortar, mud, clay, sand, gravel, shells, rotten wood, cloth, garments (the writer met one boy who had eaten three coats, thread by thread, within one year!), paper, tobacco pipes, and even mice and young rats. Salivation is frequent. Flatulence and heartburn are common. Nausea is frequently reported. Vomiting may occur. Pain and tenderness in the epigastrium are mentioned by nearly all observers; Ashford, King, and Gutierrez (1904) give it as “the most constant, most suggestive, and most clearly marked of all the symptoms of the digestive tract.” It may be brought into prominence by pressing on the right hypochondrium. Constipation is common, but diarrhoea may be present. The statements by authors relative to the fæces are very contradictory. Ashford, King, and Gutierrez found blood macroscopically in only 6 cases and blood and mucus in 5 cases, out of over 22,000 fæcal examinations, statistics which are far below the conditions observed in the Southern Atlantic States by the writer. Leichtenstern has suggested that the blood is more likely to appear during the period of copulation of the worms. Whatever the conditions are which have determined the divergent observations, evidence shows that in some cases blood may be absent, in other cases present, either macroscopically or microscopically, in the stools.

Circulatory System.—Heart: The apex beat is pronounced in the slight grades of the disease; in moderate grades it is often displaced downward and to the left; in marked grades, a notable phenomenon is the great reduction in the force of the apex beat, which is replaced by a wavy, indefinite pulsation in the epigastrium, or a tumultuous heaving of the whole pericardium and in these cases cyanosis, chiefly in the lips, is likely to be noticed; a presystolic thrill is not infrequent in moderate cases, more common in marked cases; in moderate cases, hypertrophy, especially of the left ventricle, causes an enlargement of the heart area, the murmurs are best heard in the third intercostal space; in moderate cases, hæmic murmurs are almost always present (Ashford, King, and

Gutierrez). Palpitation occurs early and is very prominent and constant. Dyspnoea is very common, especially in the later stages. The pulse varies from 80 to 132, without any necessary relation to the temperature; in the later stages it becomes dicrotic, then weak and compressible, finally thready, irregular and intermittent.

Blood.—The anaemia is the most pronounced symptom and has been taken as basis for a number of the vernacular names of the disease (miner's anaemia, brick-maker's anaemia, etc.); it is natural that recent authors have conducted special studies on the blood. Ashford, King, and Gutierrez (1904) especially have made a faithful study of the blood conditions. In one series of 540 persons, compared as to race, they found the average *haemoglobin* at over 45 per cent. in whites, over 44 per cent. in mulattoes, and over 49 per cent. in negroes. In a series of 577 persons compared, in reference to sex, the males showed an average of 41 per cent. *haemoglobin*, females 48 per cent. As extremes, 8 per cent. and 101 per cent. are reported, while special selected cases ranged from 9 to 65 per cent., with an average of 24.38 per cent. Of one series of 579 cases, the *haemoglobin* upon later examination during treatment showed an increase in 371 cases from 1 to 71 per cent., average 21.34 per cent.; 45 cases lost from 1 to 16 per cent., average 5.04 per cent.; 7 cases neither gained nor lost; a weekly increase of 20 to 30 per cent. was not rare. During the disease, the *haemoglobin* falls before the red cell count and may reach as low as 30 per cent. before much change in the reds is noticed; under treatment the reds usually increase more rapidly than the *haemoglobin*.

The red cells vary from 754,000 to normal according to conditions; of 61 special cases, the average was 2,406,416; as the disease progresses, the cells become polychromatophilic and show poikilocytosis; under treatment the red cells increase very rapidly, reaching or exceeding normal sometime before the *haemoglobin*. In 42 treated cases with a final average of 100 per cent. *haemoglobin*, the red cells averaged 5,624,197. *Leukocytosis* was not met with in Porto Rico; the majority of cases showed 5,000 to 10,000 leukocytes, and in chronic cases of long standing leukopenia was often found; the average white count of 61 cases was 8,009 on admission; during treatment 42 cases increased to 9,041 whites, 16 cases to 7,533 whites, and 3 fatal cases increased to 14,133. The *eosinophiles* present special interest: very severe chronic cases with poor resisting power and exhausted blood-making organs have little or no eosinophilia; a rise in eosinophiles is of good prognostic import; if very severe cases, presenting little or no eosinophilia, show a fall in the eosinophile count, the prognosis is not generally good; in general, good resistance to the toxin of hookworms is expressed by eosinophilia; the "special" cases gave an average of 10.8 per cent. before treatment, and 13.2 per cent. after treatment. In 29 cases, before treatment, the differential leukocyte count averaged as follows: eosinophiles, 17.1 per cent.; polymorphonuclears, 54.5 per cent.; small lymphocytes, 16.3 per cent.; large lymphocytes, 8.6 per cent.; other leukocytes, 3.5 per cent.

Respiratory System.—The respiratory symptoms are not characteristic. Patients may complain of difficulty in breathing, especially after exertion.

Temperature.—This may be normal, subnormal, or reach 100° to 102° F. Fever at the onset is said to be a fairly constant symptom in Porto Rico.

Nervous System.—The effect of uncinariasis upon the mental condition is marked; the infected children, of school age, are greatly handicapped by it in their studies; in severe cases, there is a noticeable delay in answering even simple questions and some of the patients are more or less stupid. Mental lassitude, headache and dizziness are frequently noticed; the patients may be more timid and emotional than normal; the patellar reflex is diminished or suppressed; tingling and formication are common; either insomnia or somnolence may be marked; dizziness is common, especially upon rising suddenly to the feet; joint-pains are also very frequent.

Muscular System.—The muscles are soft and flabby, and the patient is naturally weak; he tires easily, is obliged to rest after slight exertion and a feeling of lassitude is experienced which, in absence of severe symptoms, may seem unexplained; as a result, persons who are not acquainted with the true condition attribute it in the less evident cases to laziness, and there is no doubt but that much of the alleged laziness in infected districts is simply the natural lassitude connected with uncinariasis. A person with a hæmoglobin of 30 to 60 per cent. and a subnormal blood count as a result of hookworm infection cannot be expected to be vigorous, any more than a person with this condition of the blood as a result of other infection.

Urinary System.—The urine varies from 1,010 to 1,015 in specific gravity, is pale, neutral or alkaline, rarely acid, and is increased in amount.

Genital System.—In case of infection before puberty, delayed development may be very marked. Menstruation is delayed several years beyond the normal and may be more or less irregular, or absent, especially in summer. Abortions and miscarriages are frequent. Sterility and impotence are common.

Lethality.—The writer cannot state the average lethality of untreated cases in the United States, but Ashford, King, and Gutierrez (1904, p. 88) after a most careful study of the subject, express the astounding—yet probably correct—opinion that 30 per cent. of the deaths in Porto Rico are due to uncinariasis! The Porto Rico Commission treated 5,490 cases, with the following results: cured, 2,244 cases, or 40.8 per cent.; practically cured, 377 cases, or 6.8 per cent.; improved, 1,727 cases, or 31.4 per cent.; result not recorded, 522 cases; never returned, 224 cases, and ceased to return, 283 cases, total 18 per cent.; unimproved, 86 cases; died, 27 cases, or 0.5 per cent. Sandwith (1894, pp. 16–17) states that of the patients nominally under his care, 89.5 per cent. were cured or greatly relieved, 2.5 per cent. were not relieved, 8 per cent. died.

Pathology.—Aside from the anæmic conditions, attention may be directed to the intestinal tract. The stomach is usually dilated and exhibits a chronic catarrh. The small intestines, especially the jejunum and ileum, show a diffuse catarrh of variable severity, and the bites made by the worms; hemorrhages may be present or absent; there may be large spots of hemorrhagic infiltration with a worm hanging from its centre; there is a chronic interstitial inflammation; Ashford, King, and Gutierrez report the intestinal wall as very much thinned but several authors report

it as very much thickened; constrictions have been reported in South American literature.

The parasites injure in different ways, but evidence seems to be accumulating in support of the view that it is their toxic effect which is the most serious. Loeb and Allen J. Smith have shown that hookworms produce a substance which inhibits the coagulation of the blood.

Economic Importance.—A person who has not been in an uncinariasis district and who has not seen the extent of the cases, the way the people live, or rather exist, how they attempt to work, how little they accomplish compared with what they might do if they were healthy, how the mental faculties are dulled, how backward the children are, how exhausted the laborers become and what a change takes place in them during and after treatment, may find it difficult to grasp the full economic importance of this malady. As stated by the writer in 1902, it was "exceedingly difficult to escape the conclusion that in uncinariasis, caused by *Uncinaria americana*, we have a pathological basis as one of the most important factors in the inferior mental, physical and financial condition of the poorer classes of the white population of the rural sand and piney wood districts visited. This sounds like an extreme statement but it is based upon extreme facts." Since this statement was published many southern physicians have either stated or written that they are of the same opinion. The economic importance of the malady in Porto Rico, as depicted by the Porto Rican Commission must be accepted as not being exaggerated; and as observations in the United States multiply, what once seemed an extreme opinion is now rapidly becoming a very conservative view.

The importance of the disease in the cotton mills is not to be underestimated. The typical cotton mill "anæmic," of whom the writer has seen a number in different parts of the South, is a diagram of medium uncinariasis. From a purely financial point of view, it would pay the cotton mills to compel all candidates for positions to submit to microscopic examination for diagnosis, and, if infected, also to treatment, before they are given employment. Whether the American coal mines will experience a repetition of the sad and expensive history European mines have had from hookworm disease, will depend primarily upon the sanitary regulations they enforce.

Diagnosis.—In severe cases, a diagnosis upon symptoms can be made with a very high probability of correctness by anyone who is familiar with the disease. A positive diagnosis may be made in either of two ways: (1) Examine the faeces microscopically to find the eggs¹; or (2) give an anthelmintic experimentally and examine the stools for the adult worms.

Blotting-paper Test.—For persons who have no microscope a very simple test may be made with filter-, blotting- or ordinary newspaper. Fold an ounce or so of faeces in the paper and allow it to stand for several hours, then unwrap and examine for a blood stain.

¹Recently, Bass, (1906) has suggested a new method for concentrating the eggs. He shakes thoroughly a portion of faecal matter in a test tube, or similar receptacle, filled nearly to the top with a nine-tenths saturated solution of salt in water. As the specific gravity of the eggs is less than that of the salt water, they float to the top. This procedure has been tested by the writer several times and the observations confirmed. The method takes more time, however, than does the ordinary examination of slides, but in some cases may be more satisfactory.

Several authors who have criticized this test, seem not to have understood why it was suggested and have objected that it is open to error. Certainly it is open to error, the same as are numerous other tests, but in not a few cases it is an additional link in the evidence-chain, exactly as the anæmia, the dirt-eating, the red cell count, etc., and for the "country physician" who probably owns no microscope, and who is perhaps fifty miles away from any one who does, it forms an additional clue. The writer has found it useful upon a number of occasions, even when a microscope was at hand, but it is self-understood that a rough test of this kind is not to be given much weight when a better test can be made, neither is a negative result with it to be accepted as final.

Treatment.—The usual drug used in uncinariasis is either thymol or male fern and recently beta-naphthol is springing into popularity.

Thymol.—As the parasites are more or less protected by the mucus in the intestine, this should be removed by administering magnesium or sodium sulphate, or other purge, the evening before the anthelmintic is taken. Early the next morning, say at eight o'clock, give (adult dose) 2 grams (30 grains) of finely powdered thymol in capsules; at ten o'clock, repeat this dose; at noon, administer another dose of salts. The size of the dose should be modified according to the age or the condition of the patient. Ashford, King, and Gutierrez, on the basis of an experience with 12,330 doses, state that in general 0.5 gram (7.5 grains) may be given with good results to children under five years; 1 gram (15 grains) between five and ten years; 2 grams (30 grains) between ten and fifteen years; 3 grams (45 grains) between fifteen and twenty years; 4 grams (60 grains) between twenty and sixty years; 2 or 3 grams (30 to 45 grains) above sixty years; and in common with other clinicians they warn that certain conditions as great debility, very old age, pregnancy, advanced cardiac or other organic disease, a tendency to vomit, anasarca, chronic diarrhœa and dysentery are unfavorable to the administration of thymol. This medication is carried on one day per week until the patient is cured.

It is in the interest of safety not to allow or give by mouth any alcohol, oil or other solvents of thymol on the day of treatment. If stimulants are necessary, they may be given hypodermically.

Many authors warn about the ill effects of thymol. The Porto Rican Commission, after administering 12,330 doses *seems* to incline to the view that these warnings have been exaggerated and states that, "under certain precautions," they "came to know that thymol was an exceedingly in-offensive drug." Still, they warn of certain ill effects in some cases (especially with chronic enterocolitis, oedematous patients, etc.), and while they state that they had no deaths directly attributable to thymol, it might perhaps be legitimately recalled that of 4,482 persons treated at Utuado, 224 patients, or nearly 5 per cent., never returned to the clinic after their first medication. Whether a history of any of these 224 cases would have modified the conclusions reached is not altogether clear, but so far as known (even with the unusually efficient check on deaths occurring on the island) none of these patients died.

The Porto Rican Commission is entirely in harmony with the exception taken by the writer to the apparently prevailing opinion of English writers that large doses of thymol must necessarily be given. If a patient cannot stand a large dose, smaller doses will expel a few worms and thus

enable him gradually to reach a condition in which the dose may be increased.

Of 4,630 Porto Rican patients treated with thymol, the worms were entirely expelled in 3,630 cases: 1 treatment was required in 1,518 cases; 2 treatments in 1,166 cases; 3 treatments in 518 cases; 4 treatments in 247 cases; 5 treatments in 104 cases; 6, in 47 cases; 7, in 19 cases; 8, in 6 cases; 9, in 3 cases; 10, in 1 case; and 11, in 1 case. The number of doses varied, of course, with the severity of the case.

Beta-naphthol.—Bentley (1904) abandoned thymol two years ago in favor of beta-naphthol. This he has now used in several thousand cases with excellent results. The Porto Rican Commission¹ used it with success in several cases. The drug is used in the same way as thymol, but with doses one-half as large (total of 2 grams—30 grains, instead of 4 grams—60 grains).

Extract of Male Fern.—This drug has been used successfully in thousands of cases of hookworm disease. With thymol producing less serious effects than male fern, the former drug should, however, be shown preference. If it fails, male fern can be used. The dose is 4 to 8 Ce. (about 1 to 2 fluid drams) followed by salts or calomel and salts.

Eucalyptus Oil and Chloroform.—In severe cases, especially when the patients are weak, Phillips (1905) favors the following formula: Eucalyptus oil 2. to 2.5 Ce., chloroform 3. to 3.5 Ce. and castor oil 40. Ce. This is divided into two or three doses, according to the age and condition of the patient, and these are given twenty to thirty minutes apart, beginning early in the morning, fasting; should any depression occur after the first dose, the later doses are omitted. Particular stress is laid on the inclusion of chloroform in the formula, as three cases in which positive diagnoses had been made, were unaffected when chloroform water was, in error, substituted.

The writer has used this treatment on only one occasion and then unsuccessfully (as the patient was severely nauseated) and accordingly, is not in a position to form a valid judgment on this formula.

Prevention.—Since the fæces of hookworm patients represent the potential infection in concentrated form, it is clear that a proper disposal of the discharges is the great factor in preventing hookworm disease. Build proper privies and insist upon their being used; in mines, adopt the pail system. This one line of prevention, if carried out, is sufficient to blot hookworm disease out of existence, for fortunately we do not have to deal with any specifically identical infections in any of the domesticated animals.

Numerous other preventive measures have been advanced, but while good in themselves, they fail to reach the source of the evil. The proposition to wear shoes and thus prevent ground itch is of course a very good one, but financial considerations inhibit its universal adoption; if the infected fæces are properly disposed of, ground itch will practically disappear even if shoes are not worn. The proposition to drink boiled or filtered water is an excellent one, but of impracticable general

¹ According to their most recent results (1905), it is not quite so efficient as thymol; it is more necessary to thoroughly clean the intestine before using it; its systemic effects are however less marked, although its effects on diseased kidneys seem to be more marked.

application among the poor; but if the fæces are disposed of, the danger of infecting the water is removed. To keep the hands clean is of course an excellent plan, but unfortunately one of limited application. The great principle is to prevent the dirt from becoming "dirty"; clean dirt is not dangerous.

Strongyloidosis.¹—Infection with *Strongyloides stercoralis*.—**Geographical Distribution.**—The distribution of this infection is much more general than was formerly supposed; it seems to be especially a tropical and subtropical species, but as such probably encircles the earth. American cases have been found, locally, as far north as Baltimore and imported cases even further north. European cases have been found as far north as Belgium, England, Germany, and Holland, and the infection is also reported for Siberia. In Asia it is known for China, India, and Japan. In Africa it is known for Egypt. In South America it extends into Brazil. In general it follows the distribution of hookworms in man, and is very common in Porto Rico.

Zoölogical Distribution.—Strong (1901) reports this parasite for monkeys as well as man, and he was able to transmit the disease to monkeys by feeding infected human excreta to them.

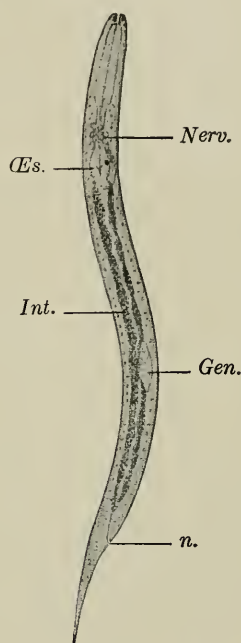
The Parasite.—I. (a) The *parasitic* (intestinal) *adults* are parthenogenetic females, measuring 2.2 to 3 mm. long by 34 to 70 μ broad, with an œsophagus about one-fourth as long as the body; a double uterus is present, each horn containing a moderate number (3 or 6) of segmenting eggs (50 to 59 by 30 to 34 μ) which escape through the vulva, situated in the posterior third of the body. These eggs are deposited in the intestinal lumen of the host or in galleries in the intestinal mucosa made by the females, and developed into—

(b) *Rhabditiform embryos*, 200 to 240 μ long by 12 μ broad, which may grow to 450 to 600 μ long by 16 to 20 μ in diameter by the time they are discharged with the fæces. The buccal

cavity is short, relatively broad, and without thickened chitinous lining. These embryos then develop within two or three days into—

II. (c) *Free-living diacious adults*. The *males* measure 0.7 mm. long; the tail is curved ventrally to form a hook; spicules curved, 38 μ long. The *females* measure 1 mm. long; vulva slightly posterior of equator of the body. Each female develops 30 to 40 eggs which may or may not segment in the uterus, these eggs develop forming the—

FIG. 62.



Larva of *Strongyloides stercoralis* as found in fresh fæces; *Nerv.*, nervous systems; *Es.*, œsophagus; *Int.*, intestines; *Gen.*, genital primordium; *An.*, anus. $\times 228$. (Looss.)

¹ SYNONYMS.—Anguilluliasis, Rhabdonemiasis. See especially Strong (1901) and Thayer (1901).

(d) *Free living rhabditiform embryos*, which measure 220μ long; when they attain 550μ in length, they moult and at the same time change to—

(e) *Filariform embryos*, possessing an elongate cylindrical oesophagus about half as long as the body. This is the infecting stage, which enters man by the mouth or through the skin, reaches the duodenum and upper part of the jejunum and develops directly to (a) the parthenogenetic females.

The complete life-cycle (*a-b-c-d-e-a*) is thus an alternation of a dioecious with a parthenogenetic generation (alloigenesis) and is the cycle reported more commonly in tropical and subtropical cases. In other cases, notably in the temperate zone, an abridged cycle consisting of *a-b-e-a* may occur; in other words there is, in these instances, a tendency to a more completely parasitic life by the omission of the free-living dioecious generation.

Source of Infection.—Infection takes place in either of two ways, passively by means of contaminated food or drinking water or actively through the skin.

Frequency.—Extensive statistics of a satisfactory nature are not accessible. In general, the infection increases in frequency from cooler to warmer climates. In Washington, D. C., several cases have been known (probably none contracted within the city); the writer believes the infection is much more common in this country than is generally supposed. Powell found it in 75 per cent. of the cases of anaemia in India (Manson).

Duration.—The longevity of the individual worm is not established. Cases of infection are known of several years standing, due perhaps to reinfection. Ward (1903) suggests that the very heavy infections occasionally reported possibly point to an endless chain multiplication by means of the abbreviated cycle (*a-b-e-a*) inside the intestine.

Symptoms and Pathology.—Here again, as in so many other cases of parasitism, the literature contains extreme statements, that the parasite is utterly harmless and that it is exceedingly injurious. A number of authors, however, see in this parasite a worm which may indeed in some cases be apparently harmless, but which, when present in large numbers, may cause “clinically, an intermittent diarrhoea with intestinal disturbances, and pathologically, a catarrh of the small intestine” (Strong).

Clinical Diagnosis.—The only possible method of diagnosis is by means of microscopic examination of the feces for the rhabditiform embryo (*b*) (see p. 595). In this connection see also p. 602. In violent purging, eggs, strung together end on end and surrounded by a delicate tube, may appear in the stools.

Treatment.—Repeated doses of thymol (see p. 593) as used in hookworm infection are usually advised for strongyloidosis also, but owing to the fact that the parasites may burrow, treatment is not always satisfactory.

Ascariasis—Eelworm Infection.—Geographical Distribution.—Cosmopolitan, more in rural districts than in cities.

Zoölogical Distribution.—In many medical works including some recent editions, the authors maintain that the common eelworm of man occurs in certain domesticated animals, such as the pig, horse, cattle, etc. This view is not in harmony with the present zoölogical classification which recognizes these infections as generically identical but specifically distinct.

The Parasite.—*Ascaris lumbricoides* Linnaeus, 1758, is, in general terms, about as large as an ordinary lead pencil but tapering toward both ends; the male measures 15 to 17, even 25 cm. in length by about 3 mm. in diameter; the female is somewhat larger, 20 to 40 cm. in length by 5 mm. in diameter, and is oviparous. The worms are grayish to reddish-yellow in color; the anterior end is provided with three lips. The egg is 50 to 75 by 36 to 55 μ , unsegmented when oviposited, and provided with a thick mammillate covering, frequently tinged yellow when found in the fæces. The parasites live in the small intestine. Development is direct, without intermediate host.

Toxocara canis (Werner, 1782), the canine eelworm, is an exceedingly common intestinal parasite of dogs and cats, and 8 cases have been reported for man, the worms having been vomited in most of these instances. It measures 40 to 90 (male) and 120 to 200 (female) mm. in length by about 1 mm. in diameter, and is easily recognizable from its arrow-shaped head; the eggs are nearly globular, 68 to 72 μ , with a thinner shell than that of *A. lumbricoides*. Development is direct, without an intermediate host.

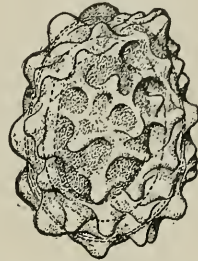
(? *Ascaris*) *maritima* Leuckart, 1876, has been reported for man but once in Greenland. One immature specimen was vomited by a child and was doubtless an accidental parasite, possibly swallowed with the entrails of some food animal.

(? *Ascaris*) *texana* Smith and Goeth, 1904, has been described as a new eelworm for man in Texas; it measured 58 to 60 mm. in length and is said to possess intermediate lips; uterine eggs segmented, 60 by 40 μ . Through the kindness of the describer, Allen J. Smith, the writer was enabled to examine the original specimens; the structures described as intermediate lips do not correspond to the intermediate lips so far as he is familiar with them in other species of *Ascaris*, but as the material was poor the writer refrains from expressing any definite opinion regarding this species, which is still *sub judice*.

Source of Infection.—The egg escapes in the fæces and slowly (in one to several months, according to conditions) develops an embryo; no intermediate host is required, at least for *Ascaris lumbricoides* and *Toxocara canis*; but when the developed eggs are swallowed, either in contaminated food or water, or from hands soiled with dirt containing the eggs, the embryo develops directly to the adult stage. Drinking water and fruits, especially, are blamed for carrying the parasite to man. Some years ago the writer bred common house-flies in a dish containing eggs of the eelworm of hogs, a parasite very closely allied to that of man, and later found the eggs in the intestine of the adult flies. It would seem therefore, that flies, by breeding in privies, might act as disseminators of the lumbricoid worm of man.

Frequency.—The eelworm is one of the most common parasites of man; it may occur at any age, from about eight months to eighty-five years, but is usually more frequent in childhood (from five to ten years)

Fig. 63.



Egg of the common ascaris (*Ascaris lumbricoides*) of man as found in fæces. Seen with superficial focus. Greatly enlarged. (Stiles.)

and youth than in adult age, and more common in women than in men. Autopsy statistics for Germany published by Heller and Müller, give the following combined results: males, 220 cases in 2,275 autopsies, or 9.67 per cent.; females, 194 cases in 1,446 autopsies, or 13.41 per cent.; children, 101 cases in 584 autopsies, or 17.29 per cent. It was present in 0.49 per cent. of 3,457 persons examined under direction of the writer. In Porto Rico, Guam, and the Philippines, it is excessively common.

Usually only from 2 to 6 individuals are present in one patient, but infections with 30, 40, 100, 140, and 300 to 600 worms are recorded, while Fauconneau-Dufresne (1880a) reports the case of a boy of twelve years who passed (chiefly by vomiting) more than 5,000 worms within less than three years, 600 being passed on one day!

In general terms, *Ascaris lumbricoides* is more common in warmer than in temperate and colder climates, and more common in the rural districts than in the cities. Authors attribute its greater frequency in rural patients to the use of unfiltered water, but other factors seem to be of more importance: in cities with a sewage system the infectious material is carried away, while in country districts the boxprivy affords greater possibilities for the spread of infection.

Duration.—The worm matures and oviposits in about a month after infection, but definite details as to the longevity of the individual parasites are lacking.

Symptoms.—Very frequently no symptoms are noticed. In other cases they are more or less indefinite, practically all of the symptoms reported for teniasis and oxyuriasis (see pp. 569, 601) being recorded for ascariasis also. For instance, among those recorded may be mentioned the following: irritation of the skin, urticaria, pallid appearance, alternate pallor and redness of the face, jaundice, dark rings around the eyes, unequal or dilated pupils, flashes before the eyes, mydriasis, amblyopia, amaurosis, strabismus, disturbances in sight and hearing, inflammation of the eye, itching of and picking at the nose, grinding of the teeth, bad taste and offensive breath, dry cough, hiccough, aphonia, anorexia, irregular or capricious appetite, dirt-eating, eructations, sensibility of stomach on pressure, nausea, vomiting, gastrorrhagia, vague abdominal pain, borborygmi, colicky pains, cramps, irregular bowels, diarrhœa, constipation, intestinal obstruction, meteorism, itching at the anus, muscular pains, progressive emaciation, headache, vertigo, fretfulness, fainting-spells, chorea, convulsions, epilepsy, catalepsy, ecstasy, hysterical conditions, eclampsia, neuralgia, paralysis, psychoses, tetanoid states, pseudomeningitis, palpitations and irregular action of the heart, syncope, etc.

While many physicians recognize the elements of danger which smoulder in an infection with ascaris, others sometimes view eelworms with little more than a passing curiosity. Hundreds of cases of ascariasis, recognized or unrecognized, may pass through a physician's hands without any fatal results being noticed. Still, the occasional danger connected with eelworms is deserving of attention. If a light infection of ascariasis is present, the chances are very great that nothing serious will result from it; but unfortunately these worms have a habit of wandering, especially in febrile conditions, and medical literature shows that it is these wanderings, even in light infections, which present the most dangerous aspect of the disease. The escape of erratic eelworms by the mouth or nose is

not very rare. If during this wandering the worm happens to come into contact with an ulcer, perforation into the abdominal cavity or the lungs may result; or the worm may enter the Eustachian tube and escape by the external ear; in some cases it enters the lachrymal duct; or it may turn at the larynx and pass a greater or less distance down the trachea and bronchi, in some cases causing suffocation, in others abscess or gangrene of the lungs; about 40 cases are recorded in which ascarids have entered the airpassages. About 90 cases are recorded in which the eelworms have wandered into the bile ducts, 9 cases into the pancreatic duct, and some 20 cases into the urinary passages. In some cases the worms pass into the abdominal cavity, either piercing the intestinal wall or working their way through an ulcer. Blanchard has compiled 81 cases in which eelworms have escaped through the body-wall; 29 cases through the umbilicus, 30 through the groin, 10 at unstated points of the abdomen, 2 by the hypochondrium, 2 by the lumbar region, 2 by an inguinal abscess, 1 each by the sacral, pubic, perineal region, and abscess of the thigh, inferior portion of thorax and linea alba. Davaine points out that, corresponding to hernia, ascarids escape by the umbilicus more frequently in children than in adults, and by the groin more frequently in adults than in children.

In view of the foregoing brief account of erratic ascarids, in not a few cases fatal, it is seen that it is at least worth while, from a prophylactic standpoint, to treat all cases of ascaris infection which are found, even independently of the question as to whether any moderate or serious local or perhaps reflex symptoms are traced to the presence of the worms in the patient under consideration. That heavy ascarid infections, such as are found in unhygienic tropical countries, may be of considerable clinical importance is evident.

Manson states that in China he treated his young patients twice a year with santonin as a matter of routine.

Diagnosis.—It is possible to make a diagnosis independently of symptoms, either by a microscopic examination of the fæces to find the characteristic eggs, or by recognition of worms passed by the anus, mouth, or nose.

Treatment.—Santonin is the classical drug for ascariasis. It is given in powder or troches, dose 0.01 gram per day ($\frac{1}{8}$ grain) for each year of the child's age, 0.06 to 0.3 gram (1 to 5 grains) for an adult. It is best given with an equal or greater amount of calomel, every morning two or three days in succession; then repeat the medication every three or four days as long as eggs are found in the fæces or until no further worms are expelled. In treating children it is well to forewarn the mothers of the possible effects of santonin upon the patient.

Among other drugs used for the expulsion of eelworms may be mentioned: oil of chenopodium, 0.13 to 0.666 Cc. (2 to 10 minims) on a lump of sugar or in emulsion, before meals for two days, followed by a purge (calomel). Fluid extract of senna, with equal parts of fluid extract of spigelia, 2 to 4 Cc. ($\frac{1}{2}$ to 1 dram) of the mixture, three times daily until purgation occurs. Thymol (see p. 593) may be used.

Serious intestinal obstruction by ascarids should be treated as obstruction from any other cause.

Oxyuriasis.—Pinworm Infection.—Geographical Distribution.—Cosmopolitan.

Zoölogical Distribution.—The pinworm of man is not known to occur in any other animal; generically identical but specifically distinct infections are, however, known for a number of mammals.

The Parasite.—*Oxyuris (Oxyurias) vermicularis*¹ (Linnæus, 1758), known as the pinworm, seatworm, also mawworm, is a small, white, roundworm measuring 3 to 5 mm. (male) to 10 mm. (female) in length, 0.16 to 0.6 mm. in diameter; the male has but one spicule; the female is provided with a relatively long, sharply pointed tail; the vulva is in the latter half of the anterior third of the body; two uteri are present filled

FIG. 64.



Embryo of the common pinworm (*Oxyuris vermicularis*) of man, in the eggshell, as found in fresh feces. (Leuckart.)

with numerous eggs, in which an embryo is developed before oviposition; these eggs are 50 to 52 by 16 to 24 μ , with thin shell, and with dorsal surface much more convex than the ventral. The earlier stages of the parasite live in the small intestine, where the worms copulate. The males are not long-lived. The fertilized females wander to the cæcum, and later when gravid to the colon. It has been maintained that the normal location for pinworms is the vermiform appendix; it cannot be doubted that pinworms do enter the appendix, for Heller, for instance, reported 36 males in 1 case; 19 males and 19 females in another; 30 males and 9 females in another; 46 males and 27 females in another; but it hardly

seems proved that the appendix is the normal habitat for these parasites. The statement occasionally found in medical works to the effect that the embryo escapes from eggs oviposited in the rectum and develops there into an adult is possibly traceable to Vix (1860); but this view cannot be accepted.

Source of Infection.—Pinworms have a pronounced tendency to wander out of the anus, and when the female is crushed by scratching with the fingers to relieve the irritation, a person naturally infects his fingers, especially under the finger-nails, with the embryo-containing eggs; from the fingers to the mouth or nose is but a short distance, and auto-infection thus occurs. Or the embryos in the bedclothes may easily soil the hands of a bed-fellow, a companion, or a nurse, and thus be transmitted to a second person. Or the eggs (free in the feces or in the body of the discharged female worms) may be transmitted to people by means of contaminated food, as uncooked fruit, vegetables, etc. No intermediate host is necessary. Theoretically it seems perfectly possible that flies may occasionally, if not frequently, play an accidental role in the dissemination of the eggs.

Frequency.—This parasite is one of the most common of the intestinal worms, varying in different autopsy statistics from 0 to over 57 per cent. It is more frequent in children (from three to ten years) and women, but has been observed in babes of five weeks up to men of eighty years. It was found in 1.3 per cent. of 3,457 persons examined under the writer's direction at the Hygienic Laboratory at Washington. Heller reports it in the proportion of 33.8 per cent. for children, 21.1 per cent. for

¹SYNONYMS.—*Ascaris vermicularis* Linnæus, 1758; *Oxyuris vermicularis* (Linnæus) Bremser, 1819; *Trichina cystica* Salisbury, 1858; *Filaria cystica* (Salisbury) Railliet, 1893, in part only (not *F. cystica* Rudolphi, 1819).

women, and 18.8 per cent. for men, in 611 autopsies at Kiel, Germany; one prominent German helminthologist has stated that he believes there are few persons who have not harbored this worm at one time or another in their lives. Further, infections are reported as more common in the spring than at other seasons of the year. The number of specimens of pinworms in one person varies from a comparatively few individuals to such heavy infections that the mucosa of the large intestine may be covered with them.

Duration.—While the longevity of the males appears to be rather limited, that of the individual female is not established. Cases of infection of ten to fifteen years and even much longer are recorded, but these are doubtless due to repeated auto-infection.

Symptoms.—Doubtless many cases of light infection pass unnoticed, and in case the person is of clean personal habits, the infection dies out. In heavy infections, however, there may be marked irritation of the intestinal mucosa, resulting in a catarrhal condition and a diarrhœa; there may be foul breath, nausea, vomiting, abdominal pain, tenesmus, deep rings around the eyes; further, one may find headache, restlessness, sleeplessness, itching at the nose, vertigo, unequal pupils, chorea, and even convulsions. One of the most constant symptoms is an intense itching and burning at the anus, due to the wandering of the female, especially shortly after the patient retires; the anus appears red, irritated, sometimes bloody; reaching the perineum the worms may pass to the vagina if the skin is moist, and may here cause hyperæmia, increased secretion of mucus, and sometimes hyperæsthesia and leukorrhœa; sexual excitement may result. Wandering pinworms have been found in the vagina, uterus, and even in the abdominal cavity.

Diagnosis.—While symptoms may indicate pinworm infection, a positive diagnosis may be made several different ways: the adult worms may be found in the stools, occasionally in considerable numbers; or they may be found in the crotch, especially if the child is examined during the restless period after retiring; a microscopic examination of scrapings around the anus (taken with a clean dull knife or a microscopic slide or other suitable object), or the cleanings from the finger-nails may reveal the characteristic eggs; finally, the eggs may be discovered by a microscopic examination of the fæces.

Opinions are divided regarding the value of the microscopic examination of the fæces; some authors consider that the eggs are not found free in the stools, while others state that they are common. The writer's experience is that the eggs may be found in faecal examinations even in some cases in which pinworm infection is not even suspected; but that a negative examination is not of much value.

Treatment.—Treatment should take into consideration two distinct points: namely, not only the removal of the gravid female pinworms from the rectum, but also the removal of the younger worms from the small intestine. A failure to consider this latter point doubtless explains not a few cases of treatment which have not met with the success the practitioner expected. Still, the emphatic statement so often met with, that persistence is an essential factor in favorable results, is often justified.

For removing the younger pinworms from the small intestine, several drugs may be used, as santonin and calomel (of each 0.05 to 0.1 gram — $\frac{3}{4}$ to $1\frac{1}{2}$ grains) given several days in succession, or large potions of an

infusion of gentian, or active saline cathartics repeated several days in succession, or thymol or beta-naphthol. Ungar gives immediately after a laxative, four doses per day of naphthalin (0.1 to 0.4 gram—2 to 6 grains) according to age, for two or three days in succession between meals.

To expel the gravid females from the rectum, rectal injections are used. An infusion of quassia seems to be one of the most popular remedies. Other commonly used enemata are: lime-water, salt and water, iced water, salt and milk (highly spoken of), cold water, aloes, diluted vinegar (which should be sterilized before using, otherwise the patient may become infected with vinegar-eels), perchloride of iron, glycerine, benzine (20 drops to a pint of warm water), finely chopped garlic with water (which has stood for twelve hours and is then strained through linen). Diluted carbolic enemata are advised by a number of authors, but they do not seem to have any special advantage over the other drugs and have in some cases decidedly poisonous effects.

The injections are given with the buttocks elevated, or in the knee-chest position, at first every evening, then every two or three or four evenings, until all evidence of worms has disappeared. If too large an injection is given to be retained this washes out a number of worms; but it should be followed by a smaller injection, two to four ounces, or an amount which can be conveniently held.

Ointments of various kinds may be applied in the evenings to the anus and perineum to relieve the itching.

Physaloptera caucasica Linstow, 1902, has been reported but once for the intestine, in Caucasus. (Length 14 [male] to 27 [female] mm., breadth 0.71 to 1.14 mm. Eggs 57 by 39 μ .)

Trichostrongylus Looss, 1905.—Three small nematode worms (*T. vitrinus*, *T. probolurus*, and *T. instabilis*¹) have been reported for man in Egypt, and one of them (*T. instabilis*) for man in Japan. They do not seem to be important parasites, so far as our present knowledge indicates, and further their normal habitat seems to be other animals (sheep, antelope, dromedary, baboon) rather than man. They measure 4 to 6 or 7 mm. in length. Their eggs might be mistaken for hook-worm eggs, but are in general somewhat larger, 73 to 90 μ long and are oviposited in the 8 to 32 cell stage.

Anguillulina putrefaciens (Kühn, 1879).—Small nematodes of various sorts frequently gain access to the stomach by being swallowed accidentally with food (vegetables, vinegar, water, etc.), and are likely to appear either in the vomit or in the feces. As an example of this sort reference may be made to *Anguillulina putrefaciens* reported by Botkin (1883) as *Trichina contorta*, in the vomit. The worms gained access to the stomach in onions and caused vomiting.

Trichocephaliasis.—Whipworm Infection.—Geographical Distribution.—Probably cosmopolitan.

Zoölogical Distribution.—The whipworm of man is also said to occur in various apes and lemurs; generically identical but specifically distinct infections are more or less common in dogs, cattle, sheep, and a number of other animals.

¹SYNONYMS.—*Strongylus instabilis* Railliet, 1893a; *S. subtilis* Looss, 1895; *Trichostrongylus subtilis* (Looss, 1895) Looss, 1905; *Tr. instabilis* (Railliet, 1893) Looss, 1905. See also Stiles, 1902, 41–42, figs. 14–21.

The Parasite.—*Trichuris trichiura*¹ (Linnaeus, 1761), the whipworm, has the general form of a whip, the posterior swollen body representing the handle, and the lash representing the slender filiform anterior portion. The male measures 40 to 45 mm., the female 45 to 50 mm. in length. The parasites inhabit the cæcum, but are occasionally found in the vermiform appendix and in the colon, rarely in the small intestine. They produce numerous characteristic eggs, 50 to 54 by 21 to 23 μ , of a yellowish to dark-brown color, with unsegmented protoplasm and with a peculiar light spot at each pole resembling apertures.

Source of Infection.—The eggs develop after being discharged in the fæces, and with the contained embryo are swallowed in drinking-water or contaminated food. An intermediate host is not necessary.

Frequency.—This is one of the most common parasites of man, varying in frequency from less than 1 per cent. up to 90 per cent. of persons examined in different parts of the world. In general terms it is more common in warmer than in colder climates. In Washington, according to examinations made under the writer's direction in the Hygienic Laboratory, and in the Bureau of Animal Industry, it is twice as common in colored as in white children; it was present in 7.69 per cent. of 3,457 persons examined by the Zoölogical Division of the Public Health and Marine Hospital Service; it may vary greatly in frequency in different wards of the same asylum; in the United States Government Hospital for the Insane 10.8 per cent. of 500 white male patients were infected, the highest percentage being 38.98 in soldiers returned from the Philippines. It is most frequent in children from three to ten years of age.

Duration.—The length of life of the individual parasite is not established.

Symptomatology and Pathology.—The medical opinions expressed regarding this worm have been too frequently characterized by extreme statements, varying from the view that it is of no medical importance whatever, to the view that is the cause of very serious disease. That, in the vast majority of cases, it is of scarcely any appreciable importance, and that its presence can not be recognized symptomatically may be conservatively admitted. But that severe infections do not produce injury is not in accordance either with probability or with recorded observations. According to some observers, the worm simply lies loose on the intestinal mucosa; but other equally competent observers report finding it with its head burrowed in the epithelium. Askanazy reports hæmoglobin in the worm's intestine, and several cases of severe anæmia have been recorded within recent years which were, apparently justly, attributed to heavy infections with whipworms.

Within the past few years Guiart, of Paris, has been defending the view that the wounds made by whipworms form the point of entrance for the typhoid bacillus; he thus attributes to whipworms a role in typhoid somewhat similar to the role played by fleas in plague. Examinations

FIG. 65.



Egg of whipworm.
× 400. (Looss.)

¹SYNONYMS.—*Trichuris* Büttner, 1761; *Ascaris trichiura* Linnaeus, 1771; *Trichocephalus hominis* Schrank, 1788; *Trichocephalus dispar* Rudolphi, 1801.

made at Washington do not bear out this hypothesis for this locality. Of 200 typhoid patients examined by the author (1907), 92.5 per cent. failed to show any intestinal worms, and the whipworm infection found was only very slightly above that of the normal population. Whipworms are supposed by some authors to be the initial cause of some cases of appendicitis.

Clinical Diagnosis.—The only method of recognizing whipworm infection is by microscopic examination of the faeces for the characteristic eggs.

Treatment.—Medical writers agree that treatment is unsatisfactory. Thymol is recommended by some,¹ but in laboratory experiments on the dog, Pfender and the writer have found it worthless in whipworm infections. In the literature on hookworm disease, frequent mention is found of the expulsion of whipworm by male fern administered in treating uncinariasis.

Hemmeter (1902) advises irrigation of the colon with benzine (1 dram of benzine to 1 quart of warm water) and at the same time internal administration of benzine.

Prevention.—A proper disposal of the alvine discharges is of first importance. Personal cleanliness, the use of proper drinking water, and the disuse of surface-water for drinking purposes, will also contribute largely to prevention.

Infection with Gordiacea.—A number of different horse-hair worms are reported as accidental intestinal parasites in the intestine of man. They are, however, rare and their effect temporary. Six cases are known for North America; in 4 of these, the parasite was *Paragordius varius*.

Infection with Thorn-headed Worms (Acanthocephali).—The thorn-headed worms differ from the nematodes in two chief characters; namely, in the absence of an intestine and in the presence of a retractile rostellum armed with hooks. An intermediate host (insects of various kinds) is required for their life-cycle. This group of parasites is of very little known importance in human medicine, but of greater importance in comparative medicine. Three species have been recorded as intestinal parasites of man, namely:

*Gigantorhynchus gigas*² (Göze, 1782), 10 to 50 cm. long; eggs 80 to 100 μ long, with three shells; very common in hogs; May-beetles and June-bugs are the intermediate host; alleged to occur in man in South Russia.

*Gigantorhynchus moniliformis*³ (Bremser, 1819), 4 to 8 cm. long; eggs 85 by 45 μ ; occurs in rats and certain other rodents; a beetle (*Blaps mucronata*) is the intermediate host; raised in man experimentally by Grassi and Callandruccio (1888e). According to Magalhães, the large roach (*Periplaneta americana*) may also serve as intermediate host.

Echinorhynchus hominis (Lambl, 1859), a doubtful species, 5.6 mm. long, reported but once.

¹Dr. Stitt, U. S. Navy, has recently expelled over 300 whipworms from one patient by using thymol. This result is much more encouraging than any similar case known to the writer.

²SYNONYMS.—*Tænia hirudinacea* Pallas, 1781; *Echinorhynchus gigas* Göze, 1782.

³SYNONYMS.—*Echinorhynchus moniliformis* Bremser, 1819.

In all these infections the diagnosis should be made by microscopic examination of the fæces to find the eggs. Treatment is the same as for *Ascaris*.

There are two other organisms (each reported but once) which have been interpreted as thorn-headed worms in man, but the cases are such that opinions differ as to whether they represent protozoa or worms in one instance, and worms or arachnida in the other.

INTESTINAL AND MUSCULAR ROUNDWORMS.

Trichinosis or Trichiniasis.—Infection with *Trichinella spiralis*.¹

Geographical Distribution.—Trichinæ are practically cosmopolitan, because of the wandering of rats; but trichinosis as a recognizable disease in man is practically limited to persons who indulge in the mis-custom ("Unsitte") of eating raw or rare pork.

Zoölogical Distribution.—From a practical, hygienic point of view, the zoölogical distribution of trichinosis extends to man, hogs, wild boars, rats, dogs, and cats. It is also reported for several other animals, such as the fox, etc., and has been transferred experimentally to several rodents (rabbits, hares, etc.) and other animals (sheep, cattle, etc.), but these exceptional infections or infections in animals not used for food do not enter largely into any scheme of prophylaxis.

The Parasite.—Three stages of the parasite should be clearly held in mind:

(a) The *adults* live in the duodenum and jejunum; the males measure 1.4 to 1.6 mm. in length by 40μ in diameter, while the females are 3 to 4 mm. long by 60μ thick; they are circular on cross section and appear as minute thread-like objects; the *oesophagus* is supported by a single row of cells known as the *cell-body*; the male is without spicules; the female is *viviparous*, the vulva being situated about one-fifth the length of the body from the mouth. The males die shortly after copulation. The females may remain for a few weeks in the lumen of the intestine, or they bore into the lymphatic spaces of the intestine where they live about five to seven weeks and deposit their numerous young, about 1,500 or more per female, namely, the—

(b) *Embryos*, which measure about 90 to 100μ in length by 6μ in breadth; these wander, either with the lymph, or with the blood, less frequently actively, to the striated muscles. They begin to reach the muscle about the tenth day after infection; they enter the muscle fibers and there develop into the—

(c) *Encysted Larvæ*.—The cysts vary somewhat in size, but are usually about 400 by 250μ . These encysted larvæ may remain alive in the muscles for years, cases being reported for as long periods as twenty to thirty-one years. The encysted worm (the "fleshworm") is the infecting stage, found in the hog; upon being swallowed in raw or rare pork, the cyst is destroyed, the larvæ pass from the stomach to the small

¹While the more commonly known name *Trichina spiralis* is not available for this parasite, it is not quite certain whether its correct name is *Trichinella spiralis* or *Trichinus spiralis*.

intestine and develop within about two days or less to the adults; the latter copulate and may have embryos in the uterus within less than a week after infection.

Source of Infection.—Leaving out of consideration the rare exceptions, and considering only the usual methods, it may be said that (*a*) *man* obtains trichinosis from eating pork; (*b*) *hogs* become infected from eating (1) uncooked swill containing scraps of pork, (2) swine offal at country slaughter houses, and (3) rats; (*c*) *rats* obtain their infection by eating (1) each other, (2) scraps of pork in houses or at meat-shops and, (3) swine offal at country slaughter houses. Thus, rats alone, swine alone, or rats and swine together, may keep up an endless-chain infection, while the infection which reaches man terminates with the death of the individual. Accordingly, man must be viewed as a more or less accidental host for the disease, while the rat, because of its cannibalistic habits, presents, theoretically, ideal conditions to serve as a normal host for this parasite.

Duration.—As a clinical combination of symptoms, trichinosis may last from a few days to several months, but usually it runs its course in about two or three to five or seven weeks; convalescence is slow and may require ten to seventeen weeks, while cases are recorded where the patients have not fully recovered from the effects for years. As an infection, on the other hand, it is reported as having lasted for five to twelve years in man and eleven to twenty-four years in the hog;¹ that is, cases are reported in which it is maintained that the encysted parasites have retained their vitality for these periods.

Symptoms.—Incubation may last from several hours to several weeks, according to the amount of infection, and according to whether a large number of parasites are ingested at one time, or whether consecutive infections of a smaller number of worms have occurred. Some infections are so light as to be entirely overlooked; other light cases, which might escape proper diagnosis, are recognized because of their contemporaneous occurrence with severe cases in the same family or among people trading with the same butcher. The more severe typical cases present Rupprecht's three more or less well-defined periods, corresponding to the three stages of the parasite and their respective location:

1. *Period of Ingression.*—The *adult* parasites are in the lumen or the tissues of the intestinal tract, hence the gastro-intestinal symptoms predominate; but in some cases these may be absent or very slight. Within a few hours to two days or so, there is a more or less heavy feeling in the stomach, with eructations; nausea develops, and the patient may vomit once or several times, or in some cases persistently for some days; the appetite is diminished, constipation, or more generally diarrhoea occurs, often with colic; the stools are at first fecaloid, but become looser even to an almost watery consistency; this diarrhoea may continue for some weeks or may give place to a more or less obstinate constipation. Muscular pains may develop early, even before the muscular tissue is invaded by the parasites; recurrent abdominal pains, especially at night and as frequently as six attacks within twenty-four hours, may develop in the

¹It is not altogether clear to the writer that this record for the hog must be accepted as absolute, for repeated infections might have occurred during these long periods.

severest cases; the extremities become cold; the pulse small and intermittent. Toward the eighth day a *temporary first œdema* of the eyelids and face may appear lasting for from two to five days. From the seventh or eighth day on, large numbers of wandering embryos are found in the peritoneal, pleural, and pericardial cavities.

2. *Period of Digression*.—This begins on about the ninth or tenth or fourteenth day, rarely as late as the forty-second day (repeated small infections?), and corresponds to the *period during which the embryos are wandering and attacking the muscles*; accordingly muscular symptoms (myositis) are the most prominent. The symptoms may be exceedingly light to severe. Certain muscles, particularly the biceps and gastrocnemius, are more firm than usual, hard and very tender, especially when the patient extends the forearm or leg. Movement may cause excruciating pain, and for relief the patient assumes a position of semiflexion. Mastication, speech, and movement of the eyes become painful; more or less complete aphonia may occur and the eyes become fixed; respiration becomes difficult, and respiratory troubles are likely to be severe, especially in the fourth and fifth weeks; there may be severe dyspnoea, accompanied by violent asthma.

3. *Period of Regression*.—All symptoms become exaggerated, and in addition the patient falls into an extreme cachexia; a *second œdema* develops about the twenty-fourth day, occurring in about 90 per cent. of the cases and attacking the head especially; hence the name, "disease of the big head," occasionally applied to trichinosis in Europe. The *larval parasites encyst* and the patient gradually recovers.

It is hardly necessary to remark that this rather diagrammatic clinical picture may vary according to the amount and number of the infections, exactly in the same way that a double tertian or a double or triple quartan malaria, or consecutive malarial infections at different hours, modify the clinical picture of malaria.

Early or late pruritus and formication may occur at certain points or over the entire body; cutaneous anæsthesia is rare. Profuse sweating is likely to occur, especially during the myositis. Stiffness of the muscles of the neck and back, extending to a distinct opisthotonos, has been recorded. Thirst is increased.

In females, anomalies occur in menstruation, and abortion is reported for some pregnant patients.

The urine decreases in quantity with the second week, but toward the fifth or sixth week and in convalescence there is polyuria. There may be an abundant sediment but the presence of *albumin is exceptional*; the urine may be intensely red in color.

As the nutrition is poor, extreme emaciation and anæmia may develop, and there may be cedema of the lungs and an obstinate bronchitis.

The mental faculties are dulled, and the patient is indifferent to what occurs in his presence. In severe cases more marked nervous symptoms develop—extreme insomnia or somnolence, delirium, etc. Opisthotonos, due to stiffness of the muscles of the neck and back, may be noticed.

Even in light cases moderate fever may be present; in severe cases it appears during the stage of ingression; the temperature rises after the beginning of the muscular symptoms, often reaching 104° F., or even

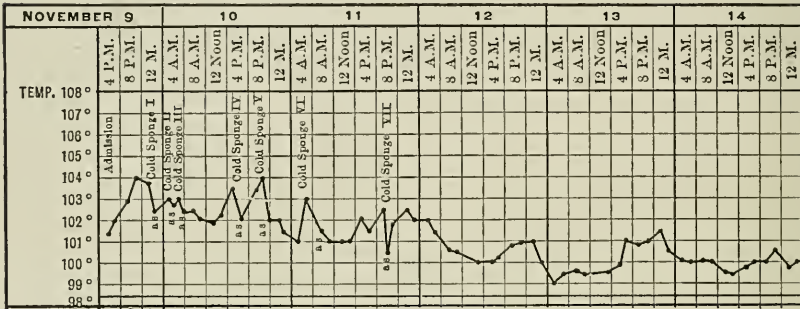
105.8° F., its duration (two or three to five or six weeks) depending upon the severity of the infection; it may be remittent or intermittent.

The pulse follows the temperature; in high fever it may exceed 100 and be extremely feeble.

The skin not infrequently shows a miliary or roseolous eruption, more rarely herpes, and the œdema is frequently followed by extensive epidemic desquamation.

Lethality.—The death-rate in different outbreaks varies between 0 and 100 per cent. Of 14,820 cases in Germany which were collected by the writer for the years 1860–97, 831 were fatal, giving a death-rate of 5.6

FIG. 66.



Temperature record in trichinosis.

per cent. The death-rate is low before the second and after the seventh week, and highest from the fourth to the sixth week, when the myositis is at its maximum.

Clinical Diagnosis.—In its severe form, trichinosis is a disease which occurs in groups of cases. In less extreme outbreaks cases may be mistaken for typhoid fever and “muscular rheumatism.” The possibility of trichinosis should always be held in mind in case of the occurrence of several typhoid-like attacks in the same family or neighborhood, or among friends (especially Germans from Saxony or Eastern Prussia), and following a celebration (wedding, birthday party, etc.) at which pork was served, or among families trading with the same butcher. When trichinosis is suspected make the following microscopic examinations:

(a) Of the pork (if any has been left) to find encysted larvæ; if these be found, chop the pork finely, wash thoroughly in water to remove the salt, and feed immediately to two or three rabbits, guinea-pigs, or white rats in order to determine whether the larvæ are alive; never use wild rats or mice for this experiment; kill one animal after two or three days and examine the contents of the upper half of the small intestine for the adult worms; kill the second animal after two weeks, the third after three weeks, and examine the muscular portion of the diaphragm for the larvæ. Even if live trichinæ are found in the intestine of the first animal, an examination of the second and third experiment animals may show that the parasites were too weak to reproduce to any extent, hence the prognosis is favorable.

(b) Upon the first suspicion of trichinosis, the patient's stools should be examined for discharged adult worms, especially if the diarrhœa is severe; dilute the faecal matter with warm water, using a rather tall, narrow graduate, or similar dish; shake well and allow the worms to settle to the bottom; pour off any matter which floats; place the sediment in a shallow glass dish so that it will not be over one-twelfth of an inch deep, and, moving it gently over a dark background, by tipping the dish first to one side and then to the other, hunt for small hair-like objects which tend to cling to the glass (if the tipping is not too rapid); place these, if found, in a drop of water on a slide, cover with a coverslip, and examine under a low-power lens.

(c) Examine the patient's blood for eosinophilia. The observations by Brown of the enormous increase in the eosinophiles has led to the recognition of many sporadic cases which otherwise would have been overlooked.

(d) If in the third week or later and diagnosis is not established, but trichinosis is suspected, excise a minute piece of the patient's deltoid; tease this on a slide, add a drop of water, or water and glycerine, flatten gently by pressure on the coverglass, and examine under low power.

Prognosis.—This is better in children than in adults, better in cases with severe diarrhœa in the early part of the disease, and good after the seventh week. If appetite, sleep, and respiration remain good, prognosis is good. Coma, delirium, and, in the last weeks, elevation of temperature and extreme dyspnœa, are bad prognostic signs. Some recover in a few weeks; in others, recovery is tedious, requiring months or several years.

Treatment.—If from the occurrence of a group of cases, or from a microscopic examination of meat, an early diagnosis is made, the stomach should be washed out immediately. In case of an early diagnosis, but at a time too late to recover the ingested undigested pork or the worms from the stomach, purge the patient with calomel, in order to remove as many of the worms as possible, for each female removed from the intestine means a reduction of the muscular infection by from 1,500 to several thousand worms. Calomel has in addition some anthelmintic property. Thymol or beta-naphthol might be administered with good effect. Unfortunately the administration of anthelmintics has not been followed by very satisfactory results, the failure being due at least in part to the sub-epithelial position of the females. No drug is known to kill the parasites in the muscles. After the parasites once leave the lumen of the intestine, all treatment must be symptomatic and supportive. Hot baths and morphine may be used to relieve pain; the profuse perspiration is relieved by atropine.

Prevention.—The German school favors a microscopic examination of pork before it is placed on sale, but statistics (Stiles, 1901) show that this system is not only very expensive but also open to many practical sources of error.

Frequent suggestions are made in American journals or text-books that we should introduce this microscopic inspection into the United States. There are, however, numerous difficulties (legal, financial, practical, and theoretical) in the way of carrying out such a plan. It would cost, in the aggregate, several million dollars per year, and that sum of money

could be spent to much better advantage in fighting tuberculosis or some other serious disease. The federal government could inspect the meat only at the registered abattoirs, and a system which has shown such poor results in Germany would certainly not appeal strongly to national, state, and local legislative bodies when the heavy appropriation was demanded. To inspect the pork in sparsely settled portions of this country is an impracticable proposition. Further, experience has shown that the microscopic inspection gives a false sense of security, and even in Germany the authorities have repeatedly felt it necessary to warn the public not to trust to the inspection, but to protect against the disease by thoroughly cooking the pork. If a Saxon or an East-Prussian desires, upon coming to this country, to bring with him his mis-custom ("Unsitte") of eating raw or rare pork, let him see that *his* pork is inspected at his own expense; but let us carefully study the German statistics before we increase directly or indirectly the taxes of the other people (who do not care to eat raw pork) in this country by supporting an uncertain hygienic measure in order that a few immigrants may please their palates with a meal of raw pork.

If pork is thoroughly cooked or thoroughly cured, there is no danger of contracting trichinosis; and since cooking and curing are methods which appeal to American and English tastes, we can well urge these upon hygienic grounds also. An extermination of rats would result in a decrease of trichinosis.

Pseudotrachinæ.—Various parasites have been mistaken for trichinæ. Thus, a sarcosporidium (*Sarcocystis miescheriana*), which is exceedingly common in pork, has been repeatedly mistaken for trichinæ, but the fleshworm is usually wound in a spiral and enclosed in a much thicker cyst, while the *Sarcocystis* is more elongate, slender, straight, and with content that appears granular under the microscope; under high power magnification, these granule-like bodies are seen to be more or less crescentic in form, somewhat similar to the crescents of æstivo-autumnal malaria. The worms described as *Trichina affinis*, *T. agilissima*, *T. anguillæ*, *T. cystica* (see p. 600), *T. cyprinorum*, *T. inflexa*, *T. lacertæ*, and *T. microscopica*, from various animals, are not trichinæ. Various strongyles also have been recorded as trichinæ. A very interesting case of pseudotrachinosis is presented in *Rhabditis terricola* (*R. cornwalli*-*Pelodera setigera*). This nematode was found in an exhumed cadaver of an English cadet, from the ship Cornwall, and was mistaken for a trichina; on the basis of this erroneous zoölogical determination, the outbreak of disease which had occurred was pronounced trichinosis and attributed to American pork.

PULMONARY ROUNDWORMS.

Metastrongylus apri (Gmelin, 1790) is a 12 to 50 mm. long thread-worm, which is rather common in the lungs of hogs. It has been reported by Diesing (1851a, 317) once for the lungs of man; Chatin (1888b) states that it also occurs in the stomach of man, but such cases are probably due to eating hogs' lungs containing the worms. Rainey's (1855) case of *Filaria trachealis* in the trachea and larynx of a human subject may

possibly belong under *M. apri*. The eggs of *M. apri* measure 50 to 100 by 37 to 72 μ , and contain an embryo at oviposition.

SUBCUTANEOUS ROUNDWORMS.

Gnathostoma siamense (Levensen, 1889) is a very remarkable nematode which has been collected on two occasions, from three similarly affected patients in Siam. It attains 9 mm. in length by 1 mm. in breadth; head globular, with 8 circles of simple spines; mouth with two lips; anterior third of body with scale-like, tridentate spines, which become smaller and more simple the farther they are from the head. The brief description by Levensen is based upon a female parasite collected from a Siamese in a superficial nodule on the side of the chest.

Rhabditis niellyi (Blanchard, 1885) is at present a nominal species which can scarcely be classified even generically with any degree of certainty. It is known only as a rhabditiform larva, 333 μ long by 13 μ broad, which was found by Nielly (1882) in cutaneous papules, chiefly on the limbs, in a boy at Brest; small worms were also found for a time in the blood, but examination of the fæces, urine, and sputum was negative. Authors have compared this case with *craw-craw*, and have explained the infection upon the assumption that the boy might have swallowed eggs in drinking water of poor quality; that the embryo then escaped and reached the blood and skin. Possibly an equally plausible explanation would be to assume a direct cutaneous infection after the manner of *uncinariasis*.

Dracunculosis¹ or Guinea-worm Infection.—Geographical Distribution.—This is essentially an Old-World infection, being found in India, Persia, Turkestan, Arabia, and certain parts of Africa. It was introduced into South America by the slaves, but does not appear to have flourished there to any great extent. Occasional imported cases are reported in other parts of the world, several being recorded for the United States (Francis, 1901a, and others).

Zoölogical Distribution.—This parasite is reported not only for man but also for cattle, horses, dogs, and several wild animals. Manson has suggested that possibly some of these cases represent specifically distinct infections.

The Parasite.—The Guinea-worm or Medina-worm, *Dracunculus medinensis* (Linnaeus, 1758), is a white to yellowish parasite, 50 to 80 or more cm. long by 0.5 to 1.7 mm. in diameter; its anterior end is bluntly rounded, with a small terminal mouth and 6 papillæ. A vulva has not been discovered, the genital organs probably discharging through the oesophagus. The intestine is rather reduced and no anus is present in adult specimens. The uterus is enormously developed and filled with sharp-tailed embryos 0.5 to 0.75 mm. long by 0.17 mm. in maximum diameter. The male is not positively known.

Source of Infection.—The embryos escape, apparently through organs prolapsed through the mouth of the adult worm, and may live in clear water for six days, in muddy water or moist earth two to three weeks; if

¹ SYNONYMS.—*Dracontiasis*; Guinea-worm disease.

slowly dried, they resuscitate in water. They may enter small crustaceans (*Cyclops bicuspidatus*, etc.), and within about three weeks develop to 1 mm. in length, casting the skin two or three times, losing the long tail, acquiring a cylindrical shape, and developing a tripartite arrangement on the tip of

the tail. They are then supposed to be swallowed in the drinking water. According to Plehn's experiments, a direct development without intermediate host is not excluded. It was formerly believed that the worm entered through the skin, and, as this mode of infection is now demonstrated for certain other worms, doubtless the possibility of this method will again be considered in connection with this species. The further history, to the gravid condition, has not been followed, but probably the worms soon leave the intestinal canal and reach the connective tissue; after copulation the male probably dies, while the gravid female, about eleven and one-half to fourteen months after infection, wanders to the subcutaneous tissue.

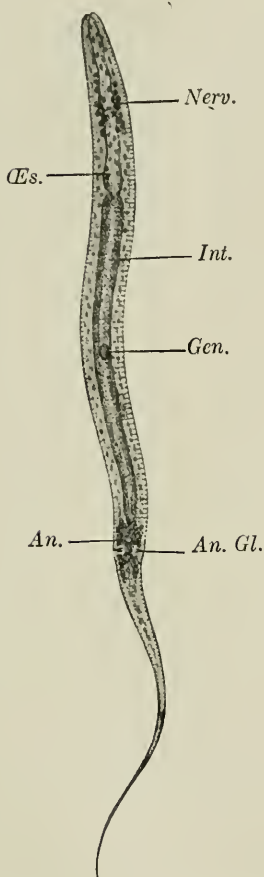
Frequency.—It is not uniformly distributed throughout the general area of infection but is especially common in some districts. In parts of Deccan, at certain seasons of the year, about 50 per cent. of the population is infected; in some parts of the western coast of Africa nearly every negro has one or more specimens (Manson).

Symptoms.—The gravid parasite produces very painful, superficial, furuncle-like swellings, chiefly on the feet and legs (about 85 per cent. of the cases), and occasionally on other parts of the body, as the back, neck, head, wrist, scrotum, penis, etc. A small blister forms and elevates the epidermis; the blister ruptures, disclosing a superficial ulcer about three-fourths of an inch in diameter, at the centre of which there is a small opening about two millimeters in diameter, from which the head sometimes protrudes. There may be fever, chill, nausea, and vomiting. The swelling may last two or three weeks; then the worm is extruded

and the wound heals; or premature death of the parasite may give rise to an abscess; or the worm may become calcified and be felt for years as a hard knot.

Treatment.—Emily's (1894a) treatment consists in injecting bichloride of mercury (1 to 1000) into the protruding worm, which can then be easily removed twenty-four hours later; or if the worm itself is not visible,

Fig. 67.



Embryo of the Guinea-worm.
Nerv., nervous system; Æs.,
œsophagus; Int., intestine; Gen.,
genital primordium; An. Gl., anal
papillæ of glandular nature
×190. (Looss.)

a few drops of the solution are injected as near the coil as possible; the parasite may then be wound out, or cut out. Another method is to protect the infected part from injury and douch it frequently with water; when this is done the uterus gradually empties and the worm may be extracted or it may come out of its own accord. Traction should not be used so long as the parasite discharges embryos, a point which may be determined by microscopic examination of the fluid issuing from the opening. The old method of extraction is to pass a coil of the parasite through the cleft end of a small stick and to wind it out of the wound *very* slowly, making only one or two turns of the stick daily. The objection to this method is that the worm sometimes breaks, the embryos escape into the surrounding tissue; violent inflammation ensues, with fever, abscess, and sloughing, and weeks or months may elapse before the patient recovers; death may occur from septic infection.

Prevention.—Upon the theory that the infection takes place through the drinking water, only filtered or sterilized water, or water of unquestionable origin should be taken when traveling in an infected region.

FILARIASIS.

Infections with Threadworms of the Genus *Filaria*.¹—The genus *Filaria* Müller, 1787, includes long, slender, filiform threadworms with curved or spiral tail. The male is smaller than the female, has 2 unequal spicules, 4 preanal papillæ, and a varying number of postanal papillæ; in the females the vulva is near the anterior end. The adults are parasitic, especially in the connective tissue, lymphatics, and body cavities; the embryo or larva frequently inhabits the blood, and in several species for which the life-history is known, insects such as mosquitoes form the intermediate host.

Quite a number of species of this genus are reported as parasitic in man, but not all of them are described with sufficient accuracy to permit a positive zoölogical determination. In medical literature the chief interest has centered around the so-called *Filaria sanguinis hominis*. As a matter of fact, the name *Filaria sanguinis hominis*, as used in literature, means but little more to zoölogists than does the expression “the tadpoles of Virginia.” We know that *Filaria sanguinis hominis* is intended to designate a young stage of a threadworm in the blood of man, the same as we know that “the tadpoles of Virginia” is intended to designate young stages of frogs found in Virginia. In recent years *Filaria sanguinis hominis* is becoming confined more and more to one species, namely, to *Filaria bancrofti*; but as a scientific name it should be eliminated from medical literature. The various young filariæ described for the blood of man may be tabulated as follows:

KEY TO THE FILARIA LARVÆ FOUND IN HUMAN BLOOD.

Sheath present:—

Periodicity absent; sheath very close; tail constricted, then sharply pointed; body 292 to 330 by 65 μ ; type locality, Manila P.I.; *F. philippinensis*, p. 624.

¹ For the most recent zoölogical summary of the species reported for man, see Penel, 1905, *Les filaires du sang de l'homme*. Paris.

Periodicity present:—

Nocturnal periodicity (?); tail truncated; 131 by 5.3μ ; type locality, Bombay; *F. powelli*, p. 624.

Nocturnal periodicity:—

Tail sharply pointed; 317 by 7.5μ ; type locality, Australia; (*F. nocturna*) *F. bancrofti*, p. 615.

Tail truncated; 164 by 8μ ; type locality, Japan; *F. taniguchii*, p. 622.

Diurnal periodicity; 317 by 7μ ; type locality, West Africa; (*F. diurna*) *F. loa*; p. 620.

Sheath absent; no periodicity:—

Tail sharply pointed:—

210 by 5μ ; type locality, West Indies; *F. demarquayi*, p. 622.

215 by 5μ ; type locality, British Guiana; *F. ozzardi*, p. 622.

Tail blunt, truncated:—

195 by 4.5μ ; type locality, West Africa; *F. perstans*, p. 622.

220 to 240 by 8 to 12μ ; type locality, West Africa; *F. gigas*, p. 624.

So far as can be discovered, none of these young worms does any appreciable injury in the blood, and of the adult worms only one, namely, *Filaria bancrofti*, can at present be viewed as serious; while a second

THE FOLLOWING IS A LIST OF THE FILARIE REPORTED FOR MAN.

ADULT WORM.	LARVA ¹ KNOWN AS—	TYPE LOCALITY AND GENERAL DISTRIBUTION.
<i>Filaria bancrofti</i> Cobbold <i>F. loa</i> (Cobbold)	<i>Filaria nocturna</i> Manson <i>F. diurna</i> Manson	Australia; tropics. West Africa; India.
<i>F. perstans</i> Manson	<i>F. perstans</i> Manson	West Africa.
<i>F. ozzardi</i> Manson	<i>F. ozzardi</i> Manson	British Guiana.
<i>F. demarquayi</i> Manson	<i>F. demarquayi</i> Manson	West Indies.
<i>F. volvulus</i> Leuckart	Gold Coast; West Africa.
<i>F. magalhaesi</i> Blanchard	Rio de Janeiro.
<i>F. taniguchii</i> Penel	<i>F. taniguchii</i>	Japan.
<i>F. equina</i> (Abildgaard)	Europe; rather cosmopolitan.
<i>F. immitis</i> Leidy	Pennsylvania; probably cosmopolitan.
<i>F. lentis</i> Diesing	Europe.
<i>F. conjunctivæ</i> Addario	Italy; Hungary.
<i>F. restiformis</i> Leidy	West Virginia.
<i>F. hominis oris</i> Leidy	Pennsylvania.
<i>F. labialis</i> Pane	Italy.
<i>F. kilimareæ</i> Kolb	Kilimara, East Africa.
<i>F. romanorum orientalis</i> Sarcani	Roumania.
[Unknown]	<i>F. gigas</i> Prout	Sierra Leone; West Africa.
[Unknown]	<i>F. powelli</i> Penel	Bombay.
[Unknown]	<i>F. philippinensis</i> Ashburn and Craig	Manila, P. I.

¹ The custom of giving to the larva a special name is not admissible under the International Code of Zoölogical nomenclature. Were we to give the egg of a mosquito one name, its larva a second, its pupa a third, and the adult a fourth, no end of confusion would result. A species is entitled to only one valid name.

species, *F. loa*, is more or less troublesome. We are hardly justified at present in assuming that all the other species are entirely without effect upon their hosts, but just what their effect is has not been shown, and whatever it may be, the indications are that at least in cases of light infection, that effect is of secondary importance when compared with *F. bancrofti*.

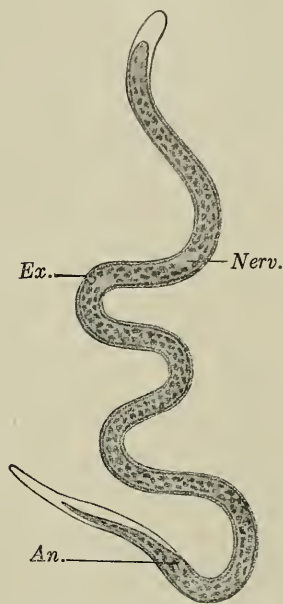
It is especially by the personal influence of Sir Patrick Manson that our knowledge of the filariæ of man has been advanced, and any article written upon the subject must necessarily be based, to no little degree, upon his work.

Infection with *Filaria Bancrofti*.—Geographical Distribution.—Australia is the type locality for this parasite, but it may be designated in general terms as a tropical and subtropical infection of Asia, Africa, and America. It is especially common on the west coast of Africa, in South China, certain parts of India, Samoa, Friendly Islands, West Indies, etc. In the United States cases are occasionally found in the Southern States; Mobile (Anderson); Charleston, S. C. (Guiteras and others); occasional cases are found further north.

Zoölogical Distribution.—The adult worm is thus far known only for man. The larva occurs in a number of mosquitoes (*Anopheles*, *Culex* and *Panoplitis*).

The Parasite.—Bancroft's filaria¹ (*Filaria bancrofti* Cobbold, 1877) is a whitish or brownish (?) transversely striated worm, 44 to 95 mm. long by 0.1 to 0.26 mm. in diameter; male with two spicules, 0.2 and 0.6 mm. long, anogenital pore 138 μ from tail, preanal papillæ uncertain, but apparently 3 pairs of postanal papillæ; vulva of the female 0.66 to 0.75 (or 1.2 to 1.3 mm.) from head, anus 225 μ from tip of tail. Viviparous. The larvæ, 300 to 340 μ long, by 6.6 to 8.5 or 11 μ in diameter, are found in the circulating blood and are provided with a sheath and sharply pointed tail; they show a more or less marked periodicity in that they are much more numerous in the peripheral circulation during the night; but if sleep is reversed to day-time, the periodicity also is reversed. Mosquitoes, while biting patients, swallow these larvæ, which then undergo development in the muscles, and finally, after fourteen to seventeen days, or, by lower

FIG. 68.



Larva of *Filaria bancrofti* in the blood of man, in Egypt. Nerv., nervous system; Ex., excretory; An., anus. $\times 514$. (Looss.)

¹SYNONYMS.—*Filaria sanguinis hominis* Lancet, Lond, 1872, Aug. 31, p. 310; larva; type locality, Calcutta (Lewis). *F. dermatemica* da Silva Araujo (1875); type locality, Bahia. *F. bancrofti* Cobbold, 1877g, July 14; adult; type locality, Australia. *F. wuchereria* Magalhães, 1877, and *F. wuchereria* da Silva Lima, 1877; type locality, Brazil. *Wuchereria filaria* Silva Araujo, 1877. *F. nocturna* Manson, 1891; larva.

temperature, up to thirty-five or forty-one days from time of infection, the worms reach a stage in which they are transmitted to man during the bite of the mosquito.

Nothing is known of the biology of the worm from the time it enters man up to the adult stage. The adult worms occur alone or as several coiled together, chiefly in the lymphatics, but also occasionally in the fluids in swollen organs. There is no satisfactory explanation, as yet, of the periodicity shown by the larva.

Source of Infection.—While it was formerly assumed that infection took place through the drinking-water, this view may now be definitely abandoned and the mosquito bite regarded as the only known or probable source of infection.

Frequency.—The frequency of the infection in man varies with the exposure to the infected mosquitoes, and this of course varies with the habits of the community, combined with proximity of mosquito-breeding places. In some places the infection is rare; in others it increases to 5, 10, 20, 50, or more per cent. of the inhabitants.

Duration.—Nothing positive is known regarding the longevity of the adult or larva, but apparently neither is very short lived.

Symptoms.—That numerous cases of infection show no appreciable symptoms is well established, but that in other cases the worms produced serious results must be admitted, especially if the adult parasites are present in large numbers or unfortunately located. According to Manson, *Filaria bancrofti* may produce the following conditions: abscess, lymphangitis, varicose groin-glands, varicose axillary glands, lymph scrotum, cutaneous and deep lymphatic varix, orchitis, chyluria, elephantiasis of the leg, scrotum, vulva, arm, mamma, etc., chylous dropsy of the tunica vaginalis, chylous ascites, and chylous diarrhœa. In not all of these cases is the exact method by which the parasites act fully understood, and the relation of the parasites to elephantiasis is based chiefly upon circumstantial evidence. In general, the adult parasites, or, Manson believes, in some cases, "their immature products of conception," cause two principal types of filariasis, one characterized by a varicosity of the lymphatics, the other by a more or less solid œdema.

The frequency of these various manifestations does not seem to be uniform in filarial patients in different geographical areas, but the reason for this variation is not at present clear.¹

Filarial Abscess.—These may be present in various affected organs and may contain the dead adult worms. They may discharge or be opened, if in the thorax or abdomen they may be serious. According to Manson, deep-seated pain in the thorax or abdomen, with inflammatory processes followed by hectic fever and a diminution in the number of or disappearance of filaria larvæ in the peripheral blood, suggest filarial abscess and indicate exploration, and, if feasible, operation.

Lymphangitis—Elephantoid Fever.—This is common in all forms of filariasis due to *F. bancrofti*; it may or may not be followed by more severe conditions, as elephantiasis, lymph scrotum, varicose glands, etc. It

¹Is it possible that local conditions, incident to the geographical distribution, have resulted in differentiating *F. bancrofti* into several subspecies, each with special tendency to a given clinical manifestation. Or have we in man even a larger number of distinct species of *Filaria* than have yet been described?

usually appears on the extremities, but may be confined to other parts of the body (groin-glands, testis, spermatic cord, or abdominal lymphatics). The attack continues for several (usually two) days, then may recur after weeks, months, or years. It begins with a severe and prolonged chill (rigor), followed by high fever, 105.8° F.; is accompanied by headache, loss of appetite, frequently vomiting, and even delirium; it ends with profuse perspiration. At the onset of lymphangitis of the extremities, the painful cord-like swelling of the lymphatic trunks and of their glands, with a red, congested streak in the overlying skin, is visible; abscess or gangrene may develop; finally the tension is relieved by lymphous discharge and the swelling partially subsides, but the skin and subcutaneous tissue do not return to quite their normal condition, some permanent thickening remaining. Elephantoid fever has been repeatedly mistaken for malaria, but a differential diagnosis should not be difficult. The filaria embryos are not always found in the blood. In treatment, elevate the affected part, compelling absolute rest; give a milk diet; use mild laxatives, cooling lotions or warm fomentations, opium to relieve pain, and scarify the swollen area if necessary to relieve tension.

Varicose Groin-glands, Helminthoma Elasticum.—These frequently accompany lymph scrotum but may occur with other filarial manifestations; the affection may be unilateral or bilateral. They are soft, doughy, obscurely lobulate, and stationary in position; but the skin may be readily moved over them. They may be easily mistaken for hernia. If the patient lies with raised pelvis the swelling slowly disappears; but if he stands erect the swelling slowly returns while the hand is pressing against the saphenous or inguinal openings. The contents are white to red, chylous, rapidly coagulable fluid, and usually contain filaria larvæ. This condition is frequently mistaken for hernia, but the swellings are not tympanitic on percussion; upon pressure they disappear slowly, and there is no gurgling; there is little or no impulse on coughing. Manson emphasizes the fact that chronic swellings about the groin, cords, testes, and scrotum in patients from the tropics should always be regarded as of possible filarial origin. They are best left alone unless they result in an incapacitating discomfort, when they may be removed. Operation is not, however, always satisfactory, as it may be followed by lymphorrhagia, excessive dilatation of some other part of the lymphatic area, chyluria, or by elephantiasis. Upon Manson's advice, Godlee, in order to prevent lymph stasis, drained the lymphatics of the region operated on into the vena spermatica and v. saphena, obtaining good results.

Superficial or Deep Lymph Varices.—These are not rare, and may be superficial on the abdomen, legs, or other parts of body; or they may be more deeply located. If they rupture, lymphorrhagia results. They may appear and disappear within a few hours, and indicate lymphatic obstruction.

Lymph Scrotum.—This is frequently accompanied by varicose groin and femoral glands. The skin is silky to the touch, but presents lymphatic varices which may open and discharge milky to bloody, rapidly coagulating lymph, usually containing filarial larvæ, which are also present in the blood. Elephantoid fever probably results from external mechanical irritation; the scrotum may become thickened, and elephantiasis may develop. In treatment, support and protect the scrotum, which should be

kept clean and powdered; but otherwise leave it alone unless inflammation be frequent, debilitating lymphorrhagia be present, or elephantiasis develops. If operation is decided upon, excise all the diseased tissue, obtaining flaps from the thigh if necessary. The patient should be warned of the possible occurrence of chyluria or of elephantiasis of the leg as a result of this surgical interference.

Chyluria; Hæmatochyluria.—This is very common, but intermittent; it may appear without warning or may be preceded by pains in the back, pelvis, and groin; the first symptoms may be retention of urine due to chylous coagulation in the bladder; the color of the discharge varies from a milky-white to a blood tinge, not only in different cases but also in the same case. It is rarely continuous; attacks occur usually lasting weeks or months or up to two years (Sheube), with more or less prolonged intervals. While not directly dangerous, the continued drain upon the system may result in anæmia, debility, depression, and incapacity for active life. Attacks are favored by pregnancy, childbirth, running, and other violent exertions which lead to rupture of a lymphatic varix in the bladder-wall.

Treatment consists in absolute rest in bed, with elevated pelvis, a light saline purge, vesical irrigation, and restriction of food (especially fats) and fluids. Various drugs (gallic acid, benzoic acid, salol, chromic acid, glycerine, tincture of perchloride of iron, methylene blue, quinine, ichthyol, etc.) have gained some reputation, but Manson is of the opinion that they have no effect whatever. Filarial larvæ may be numerous in the urine.

Orchitis.—This occurs as an acute manifestation accompanied by headache and vomiting and disappears as rapidly as it appears. It is preceded by elephantoid fever; there is a very rapid and very painful inflammation of the testes, which are much swollen; the swelling may also involve the epididymis, spermatic cord, and entire scrotum. Afterward, the fluid in the tunica vaginalis may not be entirely absorbed but may lead to chylocele. Filariae are often present in the blood. Manson suggests the possibility that the "malarial orchitis" of certain authors may in reality be a filarial orchitis.

Chylocele.—This manifestation is more or less common, either alone or more frequently with or as a result of varicose lymph glands, lymph scrotum, etc. In the morning it is always soft and it is never so tense as common hydrocele. Numerous filarial larvæ are present in the milky, reddish, quickly coagulating content. Treatment is identical with that of ordinary hydrocele.

Elephantiasis.—The recurring attacks of elephantoid or erysipelatoid fever, with resulting and accumulative thickening of the affected part, gradually give rise to an elephantiasis, which, according to Manson, is the most frequent manifestation of this filarial infection. Occasionally, however, progressive elephantiasis may occur after only one or several attacks of elephantoid fever. It is estimated that in 95 per cent. of the cases, the elephantiasis occurs in the legs, either alone or with elephantiasis of the scrotum or arms. Elephantiasis of the scrotum is also common, while that of the arms, mammæ, vulva, and limited areas of the skin (pedunculated elephantoid tumors), is more rare. In only a proportion of the cases are the filariæ found in the blood or in the fluid of the diseased organ.

The skin is rough and coarse, the hair is coarse and sparse, and the nails thick and deformed. The part pits but slightly or not at all on pressure, and does not glide over the underlying tissues. The skin is dense, fibrous, and enormously hypertrophied; the connective tissue is hypertrophied and "blubbery" from its infiltration with lymph; bloodvessels are large; the lymphatics are dilated and the lymphatic glands enlarged. As even slight injury to the affected part may induce a recurrence of the elephantoid attacks, care must be taken to protect it. Violent exercise, exposure to the hot sun, etc., should be avoided. Massage, elevation of the affected part to drain out the lymph, and elastic bandaging, are to be encouraged. Absolute rest in the recurrent attacks of fever should be insisted upon; unfortunately permanent recovery never occurs.

In extreme cases of *elephantiasis of the leg*, good results are sometimes obtained by excising a longitudinal strip 3 to 4 inches in breadth by 12 or more inches in length; during the febrile attacks, tension may be relieved by punctures with a lancet under aseptic conditions.

Elephantiasis of the scrotum frequently develops to tumors of 10, 15, 20, 40, or 50 pounds; Manson gives 224 pounds as the largest case on record. These enormous growths are unsightly and inconvenient, but not as a rule directly dangerous. Occasionally they endanger life by becoming gangrenous or by abscess formation. They may develop either rapidly, in two or three years, or very slowly. Upon reaching such a size that they are unsightly or inconvenient, surgical interference is indicated. The reader must be referred to works on surgery or to special papers on this subject for the full technique of operation. In brief, the scrotum is drained by suspension, and the position of the testes determined, also of hernia, if present; the lines of intended separation are marked and should extend only through sound tissue, since otherwise disease is very likely to occur in the scar or flaps. Perineal, pubic, and connecting cuts are made; elastic webbing is used to expel the blood; a figure-of-eight is made with rubber cord around the neck of the tumor above the guiding incisions and over the pelvis; the testes and cord are dissected out; the prepuce channel is dissected up to the pubic incision; the penis is released; the perineal and pubic incisions are deepened and the neck of the tumor is cut close to the perineum. The bloodvessels are ligated; the redundant tunica vaginalis excised; the rubber cord removed; and the flaps brought together in a T- or Y-line, the penis emerging at the point of union. The mortality of the operation should not exceed 5 per cent.

For *elephantiasis of the arm*, massage and elastic bandaging are used.

A number of authors doubt whether elephantiasis is due to *Filaria bancrofti*. The general weight of circumstantial evidence seems however to indicate that at least some cases are due to this cause, while other cases which might formerly have been attributed to this worm may perhaps be due to other causes—as streptococcus infection. Brault, for instance, recognizes a bacterial (streptococcus) and a filarial elephantiasis.

Diagnosis in General.—An attempt should always be made to find the larval filaria in the blood, urine, or chylous accumulation. There are chances for error in connection with the examination of the urine, and probably all those cases in which eggs are reported for the urine should be definitely rejected. *Trichina cystica* Salisbury, for instance, which

nearly all authors have identified with *Filaria bancrofti*, is doubtless *Oxyuris vermicularis*; vinegar eels (*Anguillula aceti*) have also been mistaken for filariæ.

Blood.—The lymphocytes increase to 24 or 40 per cent.; the eosinophiles to 8 or 18 per cent.

Treatment in General.—It is quite generally admitted that treatment to exterminate the larvæ in the blood is not only rather unsuccessful but also unnecessary. Authors have claimed, however, that they may be reduced in numbers with thymol, ichthyol, etc. The writer takes exception to the view that such treatment is undesirable, if found to be practicable, as such eradication of the larvæ would naturally be an important point gained in prevention. Anthelmintic treatment, directed against the adult, is in our present knowledge not only useless, but apparently undesirable, as the dead worm is viewed as more dangerous than the live parasite.

With Manson, the symptomatic treatment is generally admitted as consisting in rest, lowering the tension of the lymphatics by saline purgatives, by appropriate food, and limitation of fluids ingested. Several drugs (potassium iodide, gallic acid, methylene blue, ichthyol, etc.) have gained a temporary reputation, but the conclusion drawn is that their administration accidentally coincided with the time of spontaneous remission.

The necessity for asepsis in operation is so self-evident that it need not be emphasized here. Manson advises postponement of operation as long as convenient, but some authors are less conservative on this point.

General Prognosis.—While filariasis is generally admitted to be a disease which cannot be absolutely cured, the prognosis in uncomplicated cases is reported as good. Even in severe infections life may not be in danger.

Prevention.—Every person who shows the filaria larvæ in the blood, independently of the fact whether any pronounced symptoms are present, should, because of the danger of spreading the infection by mosquitoes, be considered a danger both to himself and to the persons in his neighborhood. This danger can be checked by compelling him to sleep under a mosquito-bar. Thus, the rule for prevention is: protect the mosquitoes from the patient, protect the patient himself and others from mosquitoes, and destroy mosquitoes.

Infection with the Loa.—**Geographical Distribution.**—This infection is known particularly for the west coast of Africa, but imported cases are reported for other localities, chiefly in slaves or in missionaries who have visited western Africa. Ward (1906) has recently collected all of the recorded cases and has published several new cases for North America.

Zoölogical Distribution.—The loa is positively known only for man, but Blanchard states that according to Plehn (1898) the natives say that it also occurs in sheep and goats.

The Parasite.—*Filaria (Loa) loa*¹ (Cobbold, 1864) is a filiform, colorless to yellowish-white threadworm, 16 to 57 mm. long by 0.3 to 0.57 mm. in

¹SYNONYMS.—*Filaria oculi* Gervais and van Beneden, 1859; *Dracunculus oculi* (Gervais and van Beneden, 1859) Diesing, 1860; *Dracunculus loa* Cobbold, 1864; *Filaria subconjunctivalis* Guyon, 1864; *Filaria diurna* Manson, 1891; *F. sanguinis hominis major* Manson, 1891; *Filaria sanguinis diurna* Fagge and Pye Smith, 1902; *F. bourgii* Brumpt.

diameter; the cuticle is not striated but is provided with numerous wart-like structures, not known for any other *Filaria* found in man; male with lateral caudal alæ; 3 pairs of preanal pedunculated papillæ, decreasing in size from the anterior to the posterior, and two or possibly three pairs of smaller postanal papillæ; spicules unequal, 113 and 176 μ long; vulva of female 2.35 to 2.4 mm. from head; viviparous. The larva (*F. diurna*) circulates in the peripheral blood during the day, disappearing at night, and is indistinguishable morphologically from that of *F. bancrofti*. Life-history unknown.

Manson's view that *F. diurna* represents the larva of *F. loa* is not accepted by all authors, and in fact he, himself, merely suggested it as a possibility. The point raised by several authors that not all loa patients show *F. diurna* in the blood examinations, is not a very strong argument against the hypothesis, for it is perfectly possible that they were not examined at a time when the parasites were laying their young. In September, 1904, through the kindness of Sir Patrick Manson, the writer saw in London a lady who had been in West Africa and had just come to him to have a loa extracted; she also had *F. diurna* and gave a history of Calabar swelling. Other recent observations seem to raise Manson's hypothesis practically to a certainty.

Source of Infection.—This is not yet determined. There is a popular impression that infection occurs through the drinking-water, but analogy would point to some insect as intermediate host. Manson suspects that mangrove flies (*Chrysops dimidiatus*) play this role; experiments on certain mosquitoes (*Anopheles costalis* and *A. funestus*) have been negative.

Duration.—*Filaria loa* is apparently rather long-lived; it has been seen in persons who had been away from the infectious locality for from four to ten or eleven years.

Symptoms.—This parasite inhabits the connective tissue all over the body, which it traverses freely; recent observations indicate that it is quite superficial; it is seen especially around the eye in the subcutaneous fascia about the orbit, between the conjunctivæ and bulbus; it travels over the nose, in the fingers, penis, etc. It disappears from the surface in two or three days and reappears after some days, weeks, or months. Its appearance is favored by warmth and retarded by cold.

The loa causes an itching, creeping, prickling sensation, with occasional oedematous swellings and in some cases lachrymation or considerable pain; it may determine a more or less intense conjunctivitis and disturbances in vision.

Several authors have associated with loa infections the so-called "Calabar swellings"; these appear suddenly on various parts of the body as elevations about half the size of a goose-egg, or 40 to 60 mm. in diameter; they wander slowly, about 20 to 30 mm. per day, then disappear in about three days to reappear after some months or years; they are painless, but slightly irritating; do not pit on pressure, and feel "somewhat hot both objectively and subjectively"; they may occur on any part of the body, but, according to one patient, are caused by rubbing or scratching to relieve the irritation produced by the worm.

Treatment.—When the loa approaches the surface it can readily be seen beneath thin skin; for instance, in the eyelid or over the bridge of the

nose. It is then secured by means of forceps, an incision is made, and a second pair of forceps used directly on the worm; the first pair of forceps is then released and the worm drawn out with the second pair. Manson relates that the natives extract the parasite by means of a sharp thorn, or drive it into the deeper tissue by dropping a grain of salt into the conjunctival sac. He suggests the injection of bichloride of mercury (1 to 1,000) when the worm appears in parts of the body other than near the eye.

Filaria taniguchii Penel, 1905, is reported as 68 mm. long (female), 0.2 mm. in maximum diameter; the vulva is 1.3 mm. from the anterior extremity, the anus 0.23 mm. from caudal end; cuticle unstriated; anterior end with 2 pairs of buccal papillæ; eggs 40 by 25μ ; embryos in utero measure 290μ long by 7μ in diameter. The adult is found in the lymphatic ganglia. Male unknown. The larvæ show a nocturnal periodicity in the peripheral blood; they measure 164μ long by 8μ in diameter; a sheath is present, the tail is truncated. Type locality, Ama Kusha, Japan.

Filaria perstans Manson, 1891, was based upon filarial larvæ (see p. 614) found in West Africa in the peripheral circulation both night and day. Adult worms, 45 to 80 mm. long, have now been found in the fat connective tissue in upper part of the mesentery and elsewhere, which are assumed to be its adult stage. The male is said to have 4 pairs of preanal and 1 pair of postanal papillæ; in the female, the vulva is 0.6 mm. from the mouth, the anus 0.145 mm. from the tail. The head in both sexes is large and the tail is described as having 2 minute triangular projecting appendages, giving it a mitred appearance. This parasite is also reported for British Guiana.

Filaria ozzardi Manson, 1897, is reported for connective tissue in British Guiana; the worms are 38 to 81 mm. long; male without (?) any caudal papillæ; in female, vulva 0.71 mm. from mouth, anus 0.23 mm. from tail. Larvæ (see p. 614) in peripheral blood night and day. This species is not thoroughly established.

Filaria demarquayi Manson, 1895, is a threadworm which has been reported for St. Vincent, West Indies (type locality), St. Lucia, Dominica, and Trinidad. The male is not known. The female measures 65 to 80 mm. long by 0.210 to 0.250 mm. in diameter; the vulva is 0.76 mm. from the mouth; anus 0.25 mm. from the tail; it lives in the subperitoneal connective tissue and is known only for man. The embryo lives in the blood, is 200 to 210μ long by 5μ in diameter, without sheath; the tail is sharply pointed; movements are very active; they do not exhibit any daily periodicity. The life-history is unknown and experiments on mosquitoes have thus far been negative.

Filaria volvulus Leuckart, 1893, has been reported in subcutaneous tumors, from 5 patients from West Africa. The male measures 30 to 35 cm. long, and has two unequal spicules (Prout), 82 and 177μ long; tail strongly incurved. The female measures 60 to 70μ , and is viviparous. The embryos are 250μ by 5 to 6μ , without sheath, and with sharp tail. These have been found in tumors, but not in the blood. According to Labadie Lagrave (1899) the worm is in a lymphatic canal.

Filaria magalhãesii Blanchard, 1895, has been found but once, in the left heart of a child in Rio de Janeiro. The male is 83 mm. long, with 4 preanal and 4 postanal peculiar papillæ, with scalloped outline;

shorter spicule 0.23 mm. long, longer spicule not measured; female 155 mm long; vulva 2.56 mm. from head; cuticle with transverse striation. Nothing is known regarding the life-history or medical importance of this worm.

Fuaria conjunctivæ Addario, 1885, is a filiform, 5.5 to 16 cm. long, white to brownish nematode which occurs in the eye and ligamentum gastro-lineale of man, and in the eye of horses and asses, in Europe (Italy, Hungary). Three or four cases are reported for man. Only the female parasite has been seen and nothing is known of the life-cycle.

(? **Filaria**) **labialis** Pane, 1864, has been reported but once, from the upper lip, in Naples. It measures about 30 mm. long; mouth with 4 papillæ; vulva 2.5 mm. from anus; anus 0.5 mm. from tip of tail.

Filaria immitis Leidy, 1856, is a 12-to-30-cm. long threadworm found in the right half of the heart of dogs. Mosquitoes (*Anopheles* and *Culex*) form the intermediate host. Bowlby is said to have reported its presence in the portal vein of man, but the zoölogical determination is open to question. It has been claimed that the worm in question was undoubtedly a blood fluke (*Schistosoma hamatobium*.)

Agamofilaria oculi (*F. lentis* Diesing, 1851) is a *species inquirenda*; worms varying from 1.72 to 12.6 mm. in length have been classified here; they were found in 3 cases of cataract. Errors in interpretation of supposed filariæ in the eye are likely to occur, and remnants of the hyaloid artery may be mistaken for nematodes unless a microscopic examination of the structure is made. Braun excludes the cases reported by Quadri (1857), Fano (1868a), Schoeler (1875), and Eversbusch (1891), but accepts those of Nordmann (1832), Gescheidt (1833a, p. 405), and Kuhn (1891).

Agamofilaria georgiana Stiles, 1907, is an immature worm of uncertain systematic position, found in a superficial sore on the ankle of a negress in Georgia. It measures 32 to 53 mm. long by 560 to 640 μ in maximum diameter and its mouth is surrounded with 2 small lateral papillæ and 4 large submedian lip-like papillæ.

Filaria (Hamularia) equina (Abildgaard, 1789) is a more or less common parasite in the abdominal cavity, occasionally in the pleural cavity, liver, skull, and elsewhere, of horses and asses; and several cases of its accidental presence in man have been reported. (Pleural cavity, Linstow, 1902; bronchial glands, Treutler, 1793; Brera, 1811; Blanchard, 1890a, 16.) The parasite measures 6 to 22 mm. long, and has a very characteristic blunt cephalic end, provided with two lateral semilunar lips. Its life-history is not known.

(? **Filaria**) **restiformis** Leidy, 1880, is a vivid-red worm, 26 inches long, 1.5 mm. in diameter, which is supposed to have been passed *per urethram* by man in West Virginia. Only one case has been reported and the anatomy of the worm is very imperfectly known.

(? **Filaria**) **hominis oris** Leidy, 1850, has been reported once "from the mouth of a child"; it measured 5 inches, 7 lines long, by $\frac{1}{4}$ of an inch in diameter. Nothing is known of its anatomy. It seems very possible that this may have been a *Mermis* obtained in eating an apple.

(? **Filaria**) **kilimaræ** Kolb, 1898, is at present a nominal species (type locality Kilimara, British East Africa). It attains 10 to 20 cm. in length by 0.5 to 1 mm. in diameter; is white in color, and resembles *Gordius aqua-*

ticus in general appearance, while the oral papillae are very similar to those of *Dracunculus medinensis*. Man is the type-host, and the worms are said to occur in the abdominal cavity, vomit, and stools. Kolb has classified with this form not only free-living worms but also worms which were found in hippopotamus, zebra, rhinoceros, oryx, crocodile, and fish, but undoubtedly he has fallen into error in his zoölogical determinations.

(? *Filaria*) *romanorum orientalis* Sarcani, 1888, is said to be an adult threadworm 1 mm. long, found in Roumania.

Filaria [*Microfilaria*] *powelli* Penel, 1905, is a small larval filaria reported for the blood in Bombay; it measures 131 microns long, 5.3μ in diameter, is provided with a sheath, and has a slender truncated tail; periodicity "nocturnal?"; the adult is unknown.

Filaria [*Microfilaria*] *philippinensis* Ashburn and Craig, 1906, a larval filaria found in the blood of man in the Philippines (see p. 613). Its medical importance is not yet known.

(? *Filaria*) *gigas* Prout, 1902, is based upon two embryonic filaria structures, 220 to 340μ long by 8 to 12μ broad, found in the blood of a native at Moyamba, Sierra Leone. The head is rounded, tail tapers but ends bluntly, no sheath could be seen, and the animal stained readily with fuchsin. Looss (1905, p. 170) suggests the possibility that these represent empty sheaths—namely, cast skins; Low (1905) considers that this supposed species was based upon a contamination, probably with insect hairs.

NEMATODES OF THE UROGENITAL SYSTEM.

Anguillula aceti (Müller, 1783), the vinegar-eel, has been reported several times¹ for the human bladder. It is a very small worm, 1 to 2 mm. long by 24 to 40μ broad; male with two equal spicules, 38μ long, and accessory piece; vulva near equator; embryos 222μ long by 12μ in diameter. The mode of infection has not been demonstrated, but in at least one case it was possibly by means of vaginal douches acidulated with vinegar.

No symptoms traceable to the parasite were noticed. The chief importance in connection with this parasite is the possibility of mistaking it for *Filaria*.

Leptodera pello (Schneider, 1866) is recorded (as *Rhabditis genitalis* Scheiber, 1880) as a chance parasite of the vagina and thence in the urine, in a case in Hungary reported by Scheiber (1880). The worms measure 0.8 to 1.3 mm. in length; caudal bursa of male with 7 to 10 rays each side; spicules 27 to 33μ ; vulva slightly posterior of equator; eggs 60 by 35μ . Infection may have taken place by means of poultices made of moist earth. Rhabditiform worms are also reported for the urine by Baginsky (1887b) and Peiper and Westphal (1888). Upon several occasions the writer has found rhabditiform embryos in the urine which he has been unable to identify zoölogically.

*Diectophyme renale*² (Goeze, 1782), the giant strongyle, or canine kidney-worm, measures 40 cm. (male) to 100 cm. (female) long, and is ree

¹See Stiles and Frankland, 1902, pp. 35–40, figs. 7–13; and Billings and Miller, 1902a.

²SYNONYM.—*Eustrongylus gigas* (Rudolphi, 1802) Diesing.

PLATE IX



The Kidney Worm (*Dioctophyme renale*) of Man, from a Specimen in a Dog. Natural size. Original.

in color. It is found in the kidneys of dogs and various other animals, and about a dozen authentic cases have been recorded for man. Most of the cases reported for man involve erroneous zoölogical determinations; as eelworms, clots, etc., are mistaken for the giant strongyle. Diagnosis is made by finding the characteristic eggs, 64 to 40 μ , with peculiar mosaic-like shell, in the urine. Treatment is surgical. The source of infection is not determined.

CHAPTER XXVII.

LEECHES, ACARIASIS, TONGUE WORM INFECTIONS, MYRIAPODA, PARASITIC INSECTS.

By CHARLES WARDELL STILES, PH. D., D. Sc.

INFECTION WITH LEECHES (HIRUDINEI).

THE blood-suckers resemble earthworms much more closely than they do the intestinal worms. They have a mouth at one end and a sucker at the other. The ordinary medicinal leech belongs to this group. Several species are troublesome to man, more especially in the tropics.

Limnatis nilotica (Savigny, 1820) occurs in North Africa; it is occasionally taken into the mouth with drinking-water, and it fastens in the nose, pharynx, œsophagus, or larynx. It has also been found in the vagina and on the conjunctiva. When found, it should be secured with a pair of tweezers, then injected with salt water by means of a hypodermic syringe, and removed as it loosens its hold.

Some blood-suckers, such as the Mexican *Hæmenteria officinalis*, occasionally cause symptoms of poisoning, when used to draw blood. Other leeches in certain tropical localities are said to cause considerable irritation by fastening to the body as persons walk through the grass or brush.

ACARIASIS—INFECTION WITH ACARINES.

The acarines include the mites and ticks; they have a segmented or an unsegmented body with 8 legs in the adult stage and 6 legs in the larval stage. Quite a large number of these animals attack man and animals, in some cases acting as the direct cause of disease, in other cases as the transmitter of other parasites.

Treatment.—The general rule applies that in all treatment sulphur should be used in some form, as sulphur ointment, etc., as this is particularly obnoxious to this group of parasites.

Ixodiasis—Tick Infection.—The ticks (Ixodoidea)¹ are divided into two families: the *Argasidæ*, in which the capitulum ("head") is sub-terminal in the adults, and the *Ixodidæ*, in which the head is terminal in adults. Quite a number of different species are known to attack man. In the United States the two species which have attracted the most attention within recent years are *Boophilus annulatus* (the intermediate host of Texas fever) and *Dermacentor occidentalis* (which Wilson and Chowning

¹ For the North American species, see Salmon and Stiles, 1902.

have suggested acts as the carrier of Rocky Mountain "spotted fever."¹

The Persian Argas (*Argas persicus*) enjoys the unenviable reputation in North Persia of causing a disease accompanied by extreme lassitude, fever, perspiration, severe pain, delirium, convulsions, and sometimes death. *Argas reflexus*, the pigeon-tick, attacks man, as an ectoparasite, causing a general erythema and a rapidly developing œdema.

Argas miniatus is also known to attack man.

The spinose ear-tick (*Ornithodoros megnini*) is an American species which enters the ears of cattle, deer, dogs, and swine, and occasionally of man, causing considerable suffering. It can best be removed by pouring some bland oil into the ear.

South African tick-fever is an African disease which is transmitted by ticks belonging to the species *Ornithodoros savignyi*, and is accompanied about five to ten days after the tick-bite (which causes a small swelling) by a sensation of pain and itching followed by vomiting and purging, fever and rigors, often delirium; the attack lasts about two days to a week, or fever may continue three or four weeks. This should not be confused with Anderson's tick-fever (Rocky Mountain "spotted fever.")

O. turicata and *O. talaje* are reported as ectoparasites of man in Central America, and *O. tholozani* in Persia.

Dermacentor occidentalis is known at present for the northwestern portion of the United States, from California to Montana; cases of rather severe lymphangitis and various swellings and sores developing from the bite of this tick have been seen by the writer. J. J. Buckley showed me quite a severe case, the patient having been bitten near the elbow; the arm became very much swollen, causing the patient to remain in bed for several days.

Dermacentor reticulatus, *D. electus*, *Rhipicephalus sanguineus*, *Boophilus annulatus*, *Hyalomma ægyptium*, *Amblyomma dissimile*, *A. americanum*, *Ixodes ricinus*, and *I. hexagonus* are also reported as ectoparasitic on man.

Treatment.—Ticks not infrequently hang tenaciously to the skin, but if they are covered with oil or vaseline, thus closing their breathing-pores (situated back of the fourth pair of legs), they release their hold more easily. If pulled too roughly, the capitulum ("head") is likely to break off and remain in the skin.

Sarcoptic Acariasis.—**Sarcoptic Itch.**—**Geographical Distribution.**—Judging from present records, this infection is almost cosmopolitan.

Zoölogical Distribution.—In the species *Sarcoptes scabiei*, zoölogists recognize a number of different varieties peculiar to different animals. In some cases the mites are intertransmissible between man and animals, and it is not an easy matter to distinguish between the different varieties.

The Parasites.—*Sarcoptes scabiei*,² as it occurs on man, is whitish-yellow, round to oval, with transverse rows of small spines and a number of longer bristles. In the female, both the third and fourth pairs of legs are armed with long setæ; in the male, the third pair of legs possesses setæ, but the fourth pair has a sucking-disk. The male measures 0.2 to

¹ King (1906) and Ricketts (1906) have recently succeeded in conveying the disease experimentally by means of this tick.

² See especially Railliet, 1893a.

0.3 by 0.145 to 0.190 mm.; the female is 0.33 to 0.45 by 0.25 to 0.35 mm. The parasites bore irregular galleries, 0.5 mm. to 4 or 5 cm. or more in length, in the epidermis, especially on portions of the body where the skin is thin and soft, as on the flexor surface of the carpus, between the fingers, in the groins, at knee and elbow, on penis, breast, etc., or at points subject to pressure, as at the waistband. The female is found at the blind end of the gallery; she deposits her eggs (15 to 50 in number) and faeces as she progresses. The eggs measure 140μ and hatch in four to eight days; the parasite becomes mature twenty-eight days after birth. The male dies shortly after copulation. The fecundity is very great. This species is slightly transmissible to horses, dogs, goats, and apes, but not to cats.

Sarcoptes scabiei crustosæ Fürstenberg, 1861 is associated with Norwegian itch. There is a difference of opinion as to whether this represents a distinct variety, or the ordinary itch-mite, or the itch of the wolf, which has been transmitted to man. It leads to a more severe condition than the ordinary form of itch. *S. s. equi* may be transmitted to man but the infection is short lived—about three to eight weeks. *S. s. ovis* has been transmitted from sheep to man. *S. s. capræ*, of goats, may be transmitted to man and spread from man to man. *S. s. cameli*, of the camel and dromedary, may cause a severe and persistent itch when transmitted to man. *S. s. aucheniae*, of the llama, also causes a rather serious itch on man. *S. s. suis*, of hogs, sometimes attacks man. *S. s. canis*, of dogs, when transmitted to man, may be temporary or more permanent; the symptoms are similar to those caused by *S. scabiei*. *S. s. vulpis*, *S. s. leonis*, *S. s. wombati*, and *S. minor cati*, will all develop on man, that of the cat most easily but it does not persist.

Source of Infection.—Infection takes place directly from person to person through prolonged contact, indirectly through bedclothes, towels, clothes, etc., or in other cases by direct contact in handling animals.

Frequency.—Itch seems to be decreasing in frequency. It increases during and immediately following a war. It is more especially a disease of the ignorant classes, but may appear in well-to-do persons. In some localities it is exceedingly common, and in others it appears especially among soldiers, sailors, laborers, shoemakers, and prisoners. Bulkley reports it in slightly less than 1 per cent. in 10,000 skin cases in private practice; and the American Dermatological Association, in 4.05 per cent. of about 200,000 skin cases.

Duration.—As successive generations develop in the skin, the untreated condition is not limited by the longevity of a single generation, but is potentially indefinite. It may last for years or even decades; it may disappear temporarily but not completely. Spontaneous cure is said to be unknown.

Symptoms.—The penetration of the mites (namely, in forming the galleries or burrows) causes an intense itching which leads to scratching, and increases under influence of heat, exercise, and especially when the patient is in bed. Various eruptions appear; papules, vesicles, and pustules, form. The galleries may be white, but, because of the presence of eggs and acarine excrements, they usually become grayish to blackish; these galleries are not equally distinct in all cases. Vesicles are usually present and vary in number; they appear early in the same localities as the galleries; they are transparent at the summit, rose-colored at the base, and contain

a limpid fluid; in time they dry and form a small, thin, yellowish crust; but if scratched they may become pustular. Vesicles may also appear at other places than mentioned above, as on the arms, chest, etc. The papules appear at various places on the hands, arms, etc., and are the seat of intense itching; they rapidly increase in number, but rarely attack the face.

It is stated that in 99 per cent. of cases in men lesions are found on the penis, and in 99 per cent. of cases in women, on the breast, around the nipple.

The action of the parasites is both mechanical, in tunneling through the skin, and chemical, as shown experimentally by Delafond and Bourguignon and by Hardy. Additional injury is of course incurred by scratching; sleep may be seriously disturbed by the itching; fatal cases seem to be unknown.

Norwegian itch (*scabies crustosa*) is reported for Norway, Germany, Austria, France, Denmark, Russia, Turkey, and the United States, but is rare. It is characterized by the development of adhesive yellowish or grayish crusts, in which numerous mites are found in irregular galleries. On the palms, soles, and knees, these epidermic callosities develop 1 to 6 mm.—even 12 to 30 mm.—in thickness; they may also form on the head; the hair falls; the nails thicken and become like claws, reaching 20 mm. in thickness in some cases. Cases of Norwegian itch are of long standing, three to sixteen years, and in very slovenly people. Treatment must be prolonged and energetic.

Diagnosis.—The affection is recognized from the presence of the galleries with the female at the end. These become more distinct if the part is washed. In case of doubt the parasite or its eggs may be recognized microscopically.

Treatment.—In treatment two essential points should be considered: (1) To prepare the skin so that an acaricide can act; (2) to apply the acaricide. Various modifications in technique are adopted; the following may be taken as a rather radical guide, to be modified according to facilities and according to the delicacy of the skin or condition of the patient:

1. The patient, stripped naked, is energetically rubbed all over (except the head) for twenty minutes with green soap and warm water.
2. He is then placed in a warm bath for thirty minutes, during which time the rubbing is continued.
3. The parasiticide (see below) is next rubbed in for twenty minutes and is allowed to remain on the body four or five hours; in the meantime the patient's clothes are sterilized, to kill eggs or mites attached to them.
4. A final bath is taken to remove the parasiticide.

In treating thousands of cases of acariasis (particularly the psoroptic form) in domesticated animals, it is common experience that, whatever acaricide is used, much better results are obtained if it is applied as hot as can be conveniently borne. It is also common experience that while acaricides kill the mites, they can not be depended upon to destroy the eggs; hence, time (about ten days) is allowed after the first treatment for the eggs to hatch out, but not enough time for them to become adult and begin to lay eggs; then the treatment is repeated. Lime-and-sulphur dips (one part of lime to three parts of sulphur), and tobacco-and-sulphur dips, are used; carbolic dips seem to have a greater effect upon the eggs than these, but have some objections. Hand applications are unsatisfactory.

In treating itch in man, hand applications are used. Kaposi does not consider the baths and frictions necessary. He uses an unguentum naphtholi compositum prepared as follows: adipis 100.0, sapon. virid. 50.0, cretæ præparatæ 10.0, naphthol 15.0.

Helmerich's formula (which is very irritating to the skin) is: sulphuris sublimat. 10.0, potass. carbonat. 5.0, aqua dist. 5.0, ol. amygd. dul. 5.0, adipis 35.0.

Bourguignon's ointment is composed of: ol. lavand., et menthæ, et caryophyll., et cinnamomi, each 2.0, gumm. tragacanth. 5.0, potass. carbonat. 30.0, flor. sulph. 90, glycerine, 180.0.

Hebra's modified Wilkinson ointment is made of: flor. sulph. et ol. cadini, each 180.0, adipis et sap. virid., each 500, cretæ præparatæ 120.0.

A lime-and-sulphur wash, somewhat similar to that used for sheep-scab but containing more lime, is adopted by some authors.

Demodectic Acariasis.—Infection with the hair-follicle mites.

Geographical Distribution.—Exact data on this point are lacking, but the infection is probably more or less cosmopolitan.

Zoölogical Distribution.—The hair-follicle mite, *Demodex folliculorum*, is reported not only for man but also for quite a number of animals, as dogs, cats, horses, cattle, hogs, etc. The forms which attack animals are usually considered specifically identical with that which attacks man, but as representing distinct varieties. There is some doubt at present regarding the intertransference of these varieties between animals and man; if such infection does occur it seems to be rare. The infection in dogs is the classical example of the disease; it is very difficult to cure, and quite fatal. In cattle the infection is of considerable economic importance from its effect upon the hides.

The Parasite.—*Demodex folliculorum*,¹ as found in man, is an elongate, worm-like mite, 300 to 380 μ long by 40 to 45 μ broad, with rather short, broad rostrum, and 4 pairs of short legs. It is very common in the sebaceous glands of the face, alæ of nose, lips, cheeks, forehead, Meibomian glands, and is also found in the cerumen, ventrum, dorsum, hair follicles of the chest, and at the root of the pubic hairs. In healthy glands only a few (one or two specimens) are found, but the number may increase to 15 or 20 or even many more; usually the head is toward the bottom of the follicle. This parasite multiplies very slowly, passing through the stages of egg, hexapod larva, octopod nymph, second nymph, and adult. It may live six or more days after the death of the host.

Source of Infection.—So far as known, and judging from analogy, infection may be direct or indirect from person to person.

Frequency.—Guiart (1902b) has found this parasite in all cases in which he has looked for it; Gruby found it in 40 out of 60 persons examined. It is apparently much more common in adults than among children.

Duration.—The longevity of the individual parasite is not established, so far as known to the writer, but judging from the life-cycle of the parasite a case of infection is potentially indefinite.

Symptoms.—That the effect of the hair-follicle mite has been both overestimated and underestimated is probably quite certain. The vast

¹SYNONYMS.—*Acarus folliculorum* Simon, 1842; *Demodex folliculorum* Owen, 1843; *Demodex folliculorum hominis*.

majority of cases pass unnoticed, but one case has been seen by the writer (in man) of nodular formation as large as a pea, caused by these parasites. The relation of the mite to acne is *sub judice*; that they may be one cause of acne seems, *a priori*, probable.

Treatment.—Several authors intimate that these parasites are easily killed, but in view of the difficulty experienced in treating the affection in dogs, etc., a question regarding the correctness of the interpretation in the cases in man, naturally and legitimately arises.

OTHER FORMS OF ACARIASIS.

Of the numerous other mites reported for man, probably the most important for this country are:

The harvest mites (*Leptus americanus* and *L. irritans* Riley; *L. autumnalis* Shaw, 1790, is a European species) also known as the "red bug" or "harvest bug," or occasionally as the "jigger." These are hexapod larvæ of mites, of the genus *Trombidium*. They attack man in the fields in summer and burrow into the skin, causing a very irritating sensation, and even a considerable amount of suffering, which is increased by scratching. The symptoms disappear after a few days.

Treatment.—A warm bath within a few hours after exposure; carbolized vaseline, sulphur ointment, or corrosive sublimate (2 to 1,000); extraction of the parasite with a fine needle.

Of the other mites reported for man, the following may be mentioned:

Trombidium tlalsahuatl (Lemair, 1867) occurs in Mexico, and attacks the eyelids, axillæ, navel, and prepuce, causing itching, redness, swelling, and even pus-formation; symptoms usually disappear in about a week.

The kedani mite is a Japanese acarine supposed to be connected indirectly with "river-fever"; the bacterium associated with the disease is supposed by Takana (1889) to enter through the puncture in the skin made by the mite.

Tetranychus molestissimus occurs in South America. *Pediculoides ventricosus* attacks people who handle grain.

Tydeus molestus Moniez, 1889, was probably imported into Belgium with Peruvian guano. It also attacks man.

Chicken mites (*Dermanyssus gallinæ*), and a closely allied species (*D. hirundinis*) from swallows, may attack man, causing a cutaneous eruption with considerable itching.

Holothyrus coccinella Gervais attacks birds, especially ducks and geese, in Mauritius; it attacks man, causing a cutaneous swelling with a burning sensation; it is said to enter the mouth of children.

Various mites are accidentally swallowed in food (cheese, etc.) or water, and are found in the fæces. Among the acarines reported for the fæces may be mentioned *Glyciphagus domesticus* (de Geer), and *G. prunorum* (Her).

Tyroglyphus farinæ (de Geer) attacks men handling grain; *T. longior* (Gervais, 1844) and *T. siro* (Linnæus) are reported as occurring on man or in the urine.

Histiogaster spermaticus Trouessart, 1900, is a mite reported as having been found in a cyst in the testicles; it may possibly have gained access by being introduced into the urethra in catheterizing.

Necrophagus sanguinarius Miyake and Scriba, 1893, was found dead in the urine in a Japanese case of fibrinuria with hæmaturia and chyluria; it was supposed to have come from the kidneys, but there is room for grave doubt concerning this point.

TONGUE WORM INFECTION.

At least two species of tongue worms (*Linguatulidæ*) are known to occur in man. They are not true worms, but belong to the arthropods. Neither form is especially dangerous.

Linguatula serrata Frölich, 1789, measures 18 to 20 mm. (male) long by 3 to 4 mm. broad, and 8 to 13 cm. (female) long by 8 to 10 mm. broad. The adult stage inhabits the nasal passages of canines, while the larvæ, which measure only 4.5 to 5.5 mm. long, are encysted in the liver, lungs, etc., of rabbits, cattle, sheep, and various other animals. Both the larval and the adult stages are recorded for man, especially in Europe. The larva has been found also in American cattle. In cases of nasal infection with gravid females, the diagnosis may be made by finding the four-legged embryo, enclosed in its egg-shell, in the nasal discharge; diagnosis of infection by the encysted larva is made postmortem.

Porocephalus moniliformis (Diesing, 1836) is an African tongue worm which, in the adult stage, lives in the lungs of the python. The larva lives encysted in the giraffe, *Proteles cristatus*, the mandril (*Cynocephalus mormon*), and *Cercopithecus albogularis*; it has also been reported several times for man in the liver and lungs, causing considerable irritation.

MYRIAPODA.

None of the myriapods are true parasites in man, but occasionally, though rarely, they are found as accidental parasites in the nose or intestine. Blanchard (1898c) has collected 35 such cases.

PARASITIC INSECTS.¹

Adult insects have 6 legs, and, usually, 2 or 4 wings. The larvæ are more or less worm-like, and are known as "grubs," "bots," etc. Both the larval and the adult stages may be parasitic. They are of more importance in medicine as transmitters of disease (mosquitoes and malaria, yellow fever, and filariasis) than they are as parasites (fleas, lice, grubs, etc.), and we may lay down the *general* rules that diseases (such as malaria, filariasis) which are dependent upon insects and other arthropods for their distribution, are caused by animal parasites, while those (such as typhoid) which may be disseminated by arthropods, but are not dependent upon them, are usually caused by plant parasites.²

¹See especially Osborn, 1896, "Insects Affecting Domestic Animals," *Bull.* 5, n. s., *Div. Entomol., U. S. Dept. Agric.*, Wash.

²Whether the African tick fever and the Rocky Mountain "spotted fever" form exceptions to these rules is a point for further study.

Burrowing Fleas: Jigger Flea, Chigger or Chigoe.—**Geographical Distribution.**—This is a tropical and subtropical parasite of American origin; it has now been introduced into Africa and adjacent islands, where it has spread rapidly; it is also reported for Persia, India, and China.

Zoölogical Distribution.—This parasite attacks not only man, but also horses, cattle, swine, and dogs. It is said to attack chickens and certain other birds; but, as a distinct species (*Argopsylla gallinacea*) is found on chickens and also reported as attacking man, it might be well to re-examine this infection to see whether a confusion in determination has occurred.

The Parasite.—*Sarcopsylla penetrans*¹ (Linnæus, 1758) is about 1 to 1.2 mm. long; when young, the female resembles other fleas, but, after mating, it burrows into the skin and swells into a body resembling a beet in appearance, but fortunately not in size. The males do not burrow. The eggs hatch out on the ground and the larvæ undergo a pupation or resting stage.

Frequency.—In some localities this infection is very common. Manson reports that it causes a large amount of invalidism among the coolies in East Africa. There may be only one or two parasites present, or the fleas may be so numerous and thickly set as to give the infected part a honeycombed appearance.

Duration.—The female remains in the skin about three weeks.

Symptoms and Pathology.—The fertilized female burrows into the skin, especially on the feet, but also on other portions of the body, forming small, pea-like, elevated swellings; the caudal end of the flea may be seen at the opening of the burrow. The parasite causes considerable irritation; pus forms around it; the skin may ulcerate, leaving a small sore. In extreme cases, as among very indolent negroes, the trouble may extend to the loss of toes. Bacterial infection of the wound (tetanus, etc.) may lead to serious results.

Diagnosis.—The diagnosis is not difficult. The pea-like swellings on the feet, especially under the nails and between the toes, are in themselves suspicious, and a closer examination reveals the caudal end of the parasite.

Treatment.—The entire parasite should be pried out with a sharp knife or similar instrument, when possible without breaking. Application of chloroform, or mercurial ointment may first be used to kill the flea. The wound is thoroughly cleansed and dressed.

Prevention.—The wearing of shoes in the infected districts will greatly reduce the chances for infection.

Jumping Fleas:² *Pulex* and *Ctenocephalus*.—**Geographical Distribution.**—Cosmopolitan.

Zoölogical Distribution.—Fleas are common on numerous different species of animals, and some of the species are intertransmissible between man and their normal hosts.

The Parasites.—There are two fleas in particular which attack man:

Pulex irritans (Linnæus, 1758), known as the "house flea" or "common flea," is more common in Europe than in the United States.

¹SYNONYMS.—*Pulex penetrans* Linnæus, 1758; *Sarcopsylla penetrans* (Linnæus) Westwood, 1840.

²For a zoölogical revision of the fleas, with a list of all species on various animals, see Baker, 1905, Proc. U. S. Nat. Mus.

Ctenocephalus canis (Curtis, 1826), the ordinary "cat and dog flea," seems to be more common in the United States than *P. irritans*; it differs from *P. irritans* in the presence of a comb-like structure on the first thoracic segment.

The flea-eggs develop in cracks in the floor and other suitable places. In the case of *C. canis* the egg stage lasts one day, the first larva, three to seven days, second larva, three to four days. They commence spinning from seven to fourteen days after hatching, and the imago appears five days later; thus an entire generation may develop in a little more than a fortnight.

Medical Importance.—Adult fleas may: (a) attack man as ectoparasites; (b) act as intermediate host for certain tapeworms (*Dipylidium caninum*, see p. 567); (c) act as disseminators of plague. Flea-larvæ are also reported as pseudoparasites in man.

Prevention.—Many methods are suggested to protect against the attacks of fleas, as, for instance, the use of essential oils; but the reports from their use heard by the writer are not very encouraging. A more radical method is to clear the fleas out of the house by fumigation with sulphur, by sprinkling pyrethrum powder, or by washing the floor with benzine or with hot soap-suds.

Pediculosis: Lousiness.—There are three species of lice which attack man; namely, the head-lice, the body-lice and the pubic-lice.

Geographical Distribution.—Cosmopolitan.

Zoölogical Distribution.—The three lice typical for man do not normally live on other animals; occasionally lice from various animals attack man, but remain on him only a short time.

The Parasites.—The head-lice (*Pediculus humanus*¹ Linnæus, 1758) lives among the fine hairs of the head; the female lays 50 to 60 eggs, or "nits," within six days; these white "nits" are attached to the hair, especially back of the ears; they hatch on the sixth day; the young become mature in seventeen to twenty days.

*Pediculus corporis*² de Geer, 1778, the body-lice, secretes itself in the folds of clothing, but draws its food from the body; it lays 70 to 80 eggs in the folds of the clothing; these hatch in three to four days and mature in fifteen to eighteen days.

The pubic-lice, or crab-lice, *Phthirius pubis*³ (Linnæus, 1758) is much more common on men than on women; it is found chiefly on the pubes, occasionally on the eyelashes, and is reported also for the head. It lays 10 to 15 eggs, which hatch in six to seven days and become mature in fifteen days.

Source of Infection.—Lice may pass directly from one person to another, or may be carried by flies. The beds in hotels and sleeping-cars are also sources of infection. One instance is known to the writer in which a large number of girls, in a fashionable Eastern boarding-school, developed lousiness a short time after traveling in a sleeper from Chicago.

¹SYNONYMS.—*P. capitis* de Geer, 1778; *P. cervicalis* Latreille, 1803.

²SYNONYMS.—*Pediculus vestimenti* Nitzsch, 1818; *P. tabescentium* Alt, 1824.

³SYNONYMS.—*Pediculus pubis* Linnæus, 1758; *P. inguinalis* Reichard, 1759; *Phthirius inguinalis* (Reichard) Leach, 1815; *Phthirius pubis* (Linnæus, 1758) Küchenmeister, 1855.

Symptoms.—Head-lice may cause an irritation accompanied by an eczema or pustular dermatitis. The discharge, mixed with excoriations due to scratching, mats the hair together; scabs and crusts form; if allowed to run, a regular carapace may form, called *trichoma*, and the head exudes a foetid odor. Various low plants may grow in the trichoma, the entire structure being known as the *plica palonica*.

Body-lice cause rose elevations, analagous to urticaria, and papules which become excoriated at the summit and covered with brownish crust; itching and scratching result, and white scars are found, surrounded by brownish pigment; the skin may become thickened and takes on a bronzed tinge, presenting a melanoderma which is one of the chief attributes of vagabonds' disease.

Pubic-lice cause an irritating pruritus, especially at night; a dry prurigo, represented by small rose or reddish papules; and in some cases in the subumbilical region, on the flanks and internal surface of the thigh, bluish-gray temporary spots, 7 to 8 mm. in diameter, not painful and not paling much on pressure.

Treatment.—If feasible, as in male patients, it is well to cut the hair, although this is not at all necessary. Saturation of the head with kerosene will kill the lice, but carbolic washes¹ are more severe on the eggs ("nits"). Washing with tincture of *Cocculus indicus* is advised by some authors, its advantage being the absence of odor. Combing with a fine-tooth comb is an old home-measure of relief.

The same measures may be used for the pubic-louse; or mercurial ointment may be applied. In treating for the body-louse, it is the clothes more than the body which need radical treatment. The entire clothing should be baked or boiled.

The itching may be allayed by warm baths, sodium bicarbonate being added to the water.

Bed-bugs.—Geographical Distribution.—Cosmopolitan.

Zoölogical Distribution.—The popular view that bed-bugs are carried by swallows and bats is erroneous; generically identical but specifically distinct parasites infest these animals.

The Parasite.—There are two bed-bugs which infest dwellings.

The "common bed-bug," *Cimex lectularius* Linnaeus, 1758, is too well known to require description. It is a very intelligent animal, which secretes itself in crevices, in cracks, in draperies, and around the buttons of mattresses during the day, seeking its food at night. It lays eggs from which the larval stage issues; in its development it sheds its skin, and it feeds once between every two moultings, then once again after the last moult before it lays its eggs. The odor, supposed to be peculiar to the bed-bug, is common to the entire group to which this insect belongs.

The Mexican bed-bug or blood-sucking cone-nosed bug (*Conorhinus sanguisuga*) is spreading from Mexico toward the North. The adult possesses wings. This is normally a predaceous insect rather than a parasite, and it feeds upon the bed-bug. Having tasted human blood from this source, it is now acquiring the habit of attacking man. Other species of *Conorhinus* are reported for other parts of the world.

¹A 2 per cent. carbolic solution, or any of the ordinary carbolic sheep-dips, may be used.

Frequency.—The common bed-bug varies in frequency inversely to the care exercised in housekeeping.

Source of Infection.—Bed-bugs wander from house to house, but they are usually spread through the moving of old bedding, or in clothes. The laundry is a common source of importation, especially in localities like Washington, where negroes take the laundry to their homes for washing. The writer has known of bed-bugs being carried on the coats of workmen such as carpetcleaners, paperhangers, etc., and even of well-to-do bachelors whose flats were cared for by negroes.

Symptoms and Pathology.—Aside from the fact that the bed-bug has fallen under suspicion as the intermediate host of relapsing fever, the writer is convinced that the common bed-bug may occasionally be of greater medical importance than is usually attached to it. He knows, for instance, of one case where a young man underwent treatment for neurasthenia, the diagnosis being agreed upon by several prominent clinicians; all symptoms promptly disappeared, however, immediately following a thorough fumigation of his rooms, where nearly a pint of bed-bugs was collected! The effect of bed-bugs upon delicate or young children, in loss of sleep, is occasionally a matter not to be entirely ignored.

Treatment.—Treatment of this trouble consists in removing the cause. Above all methods, the writer favors thorough fumigation of the house with flower of sulphur (2 pounds to 1,000 cubic feet of space). For practical reasons, in order not to attract attention, it is best to start the fumigation in the evening after dark. In experiments¹ in Washington, and in New Jersey, he has generally placed ordinary flower of sulphur in wash-basins, old kettles, etc., and set these dishes on bricks in larger basins or tubs containing water enough to come close to the top of the dish containing the sulphur; a small well is made in the sulphur with the finger and a small amount of alcohol poured in; the alcohol is then set on fire and the sulphur allowed to burn out. All windows should be tightly shut, and the house should remain closed for twelve to twenty-four hours. One room may be fumigated at a time if desired. Metal ornaments, clocks, fine instruments, valuable tapestries, etc., should, of course, be removed before fumigating. The sulphur odor remains in the pillows and mattresses for some days, but this objection may be obviated by sending them to a steam-cleaner instead of fumigating them.

The treatment with hydrocyanic-acid gas, as advised by the Bureau of Entomology, is too dangerous and too expensive. As the fumigation is usually carried out by women in the family, who, in their haste to leave the room when the gas is started, may trip on their dresses, fatal accidents may occur, quite aside from the injury done to rugs, etc. The sulphur fumigation does not present this danger.

The ordinary methods of washing with kerosene, gasoline, etc., are good so far as they go, but are less reliable than thorough fumigation with sulphur. A saturated solution of corrosive sublimate in water may be used in the cracks of wooden beds, floors, etc., if desired, as a general preventive.

¹There is nothing new or original in this method.—C. W. S.

Myiasis.—Dipterous Infection.—The term “myiasis” is used to denote an infection with the larval (“grub”) stage of dipterous insects. Various authors distinguish a myiasis externa and interna, *M. intestinalis* and dermatosa, or *M. cæstrosa* and muscida, the first four terms being based upon the position of the parasites, the last two on the zoölogical classification.

For American physicians, probably the most important grub-parasite is the—

Screw-worm.—*Comptosmyia macellaria* is a fly which deposits its eggs in wounds. It may also oviposit in the nostrils of persons (particularly those with offensive catarrh) when sleeping out of doors. The larva, known as the “screw-worm,” issues within a few hours, and burrows into the tissues; it feeds for five to seven days, then exits to pupate. Accordingly, in case of infection the larvæ continue their active injury for five to seven days. Infection with this larva may be serious, and in a high percentage of the cases (21 in 31, Maillard) fatal. An effort should be made to kill the larvæ; for this purpose the infected parts are douched with a 20 per cent. solution of chloroform in sweet milk, or a carbolic wash; some of the parasites may be removed with simple salt water, or with a small pair of forceps.

Dermatobia hominis is a tropical American fly, the larval stage of which is found under the skin of man and various animals. *Hypoderma bovis*, *H. lineata*, so common in the backs of cattle, and *H. diana* of deer, may also parasitize in man.

Ochromyia anthropophaga, the Cayor-worm, attacks man in Senegal. *Gastrophilus* is reported in Russia in connection with “creeping eruption.” *Sarcophaga* (flesh-fly) larvæ are found in wounds, in the nose, ears, anus, vagina, intestine, etc. Quite a number of other species are known as parasites or as pests of man.

Various dipterous larvæ are reported as chance parasites in the intestine (intestinal myiasis)¹ having been swallowed accidentally in the food or water: the common house-fly (*Musca domestica*), *M. vomitoria*, the small house-fly (*Anthomyia canicularis*, also reported for the vagina), the cheese-fly (*Piophilæ casei*), *Phora rufipes*, mosquito larvæ, and other species. In some cases these chance parasites produce considerable uneasiness or more or less serious gastric disturbance, until vomited or passed in the fæces.

Various larval insects are also found in fresh wounds, and have been especially troublesome in time of war.

Scoleciasis.—Scoleciasis is a term used to designate accidental infection with coleopterous larvæ.

Miscellaneous.—The reported cases of snakes, frogs, earthworms, etc., as parasites, are instances of spurious parasitism.

¹ For the larvæ which breed and feed in fæces, and thus come into consideration in connection with typhoid fever, see especially Howard, 1900.

PART VIII.

NUTRITION.

CHAPTER XXVIII.

GENERAL CONSIDERATION OF METABOLISM, NORMAL AND IN DISEASES.

By RUSSELL H. CHITTENDEN, PH. D., LL. D., Sc. D.,

AND

LAFAYETTE B. MENDEL, PH. D.

General Statements.—Broadly speaking, the study of metabolism embraces a consideration of the collective chemical changes taking place in living matter. The animal organism as a whole, and its component tissues and cells are the seat of incessant chemical transformations, modified in character and extent by variations in the degree of activity of the individual tissues and cells. This activity likewise implies a more or less continuous interchange between the individual cells of the body and the blood and lymph by which they are bathed. Our conception of an active tissue carries with it the idea of more or less continuous construction and destruction, accompanied by an exchange of pabulum and waste products, thereby presenting an ever varying environment. It is the purpose of this chapter in physiology to trace out the exact character of these alterations, the relationship which they bear to each other, the influence of modification in cell and tissue environment on metabolic phenomena, and the relative importance of the varied processes in health and in disease.

When the metabolic processes are constructive in character, they are termed *anabolic*; when they are destructive in character, they are called *katabolic*. Anabolism, therefore, means the building-up of the inert and dead food material into living protoplasm, which usually implies the transformation of relatively simple molecules into more complex ones. Katabolism, on the other hand, carries with it the idea of destructive decomposition or disintegration; *i. e.*, a transformation of the living protoplasm into various decomposition products, and the cleavage or breaking-down of the latter into still simpler chemical compounds, with liberation of energy. There are, however, many metabolic processes which are more

advantageously treated of under a different heading, as those of secretion, excretion, digestion, etc. These processes are strictly metabolic, involving alteration and exchange of material in individual glands or organs; but since they have to do with specific or localized functions of the body, they can be considered more appropriately in separate chapters dealing with the processes as a whole.

Metabolism is a part of that broader process or series of processes spoken of as nutrition, having to do more concisely with the changes taking place in the body other than those ordinarily classed under the head of secretion, excretion, etc. The metabolic processes are especially concerned with the life, growth, and functional activity of those organs and tissues which are preëminently associated with the maintenance of physiological rhythm. The muscle and nerve tissues are eminently the metabolic tissues of the body. The liver is preëminently a glandular organ endowed with metabolic power. The secretion of bile is in a measure a metabolic process, but we classify this phenomenon preferably under the head of secretion. The glycogenic function of the liver, on the other hand, is more appropriately classed as a metabolic phenomenon pure and simple; while the transformations of many crystalline amino-acids which take place in the hepatic cell with formation of urea are likewise typical metabolic processes. These facts are to be emphasized simply as illustrating the principle that while many processes in the body are strictly metabolic, not all are classed under this head, because of the greater convenience of treating certain of them in connection with other phenomena more easily recognizable.

It is obvious that the character of the metabolic transformations taking place in the body cannot remain exclusively of one type, if the organism or individual is to preserve its integrity and peculiar make-up. Thus, if disintegrative processes were to continue without any compensatory constructive activity, a complete break-down would occur. Under ordinary conditions, accordingly, building-up (synthetic) processes go on side by side with the disruptive changes which liberate energy. There are, however, types of organisms that are eminently synthetic in respect to the chemical changes which are inaugurated within them; this is the characteristic of plants as a class. In animals, degradative changes are most conspicuous. Nevertheless, anabolism and katabolism manifest themselves in both plants and animals; and it is merely in the preponderance of one or the other type of metabolic phenomena that any essential difference in the fundamental behavior of these living forms becomes evident.

NATURE OF METABOLISM.

A study of the products which arise in the animal body, incidental to the metabolic activities resulting in a liberation of energy, indicates that the chemical changes involved are in large part those of oxidation and cleavage. Complex molecules of fat, carbohydrate and proteid are transformed into relatively simple compounds which are uniformly richer in oxygen than the constituent components of animal protoplasm. The sulphur and phosphorus of the proteids, for example, become oxidized in their transformations within the body and reappear in the excre-

tions as salts of sulphuric and phosphoric acids. The reactions involved are generally more complex than the illustration here selected would indicate. Many substances, however, are merely split up into simpler compounds; some are subjected to hydrolytic changes without further chemical transformation; while not a few undergo a cleavage preliminary to subsequent oxidation or synthesis, or both. In thus indicating how food or tissue constituents may be burned up in the body, the analogy with the familiar combustion processes of every-day life must not be carried too far, since combustion within the animal organism is of a peculiar and characteristic type. The reactions do not proceed with the unchecked vigor manifested in the oxidation of fuel in a fire-box. In the body we are dealing with a gradual process, regulated by conditions with which we are still largely unacquainted—a succession of chemical changes rather than a sudden and continuous burning of organic materials. Whenever they occur, the oxidations are, moreover, indirect; that is, the tissue combustion nowhere proceeds through direct intermediation of the oxygen inspired and held in the circulating fluids.

It was the recognition of these facts and the demonstration that oxidative changes for the most part do not go on in the circulating medium, which led to the abandonment of the view that the blood is the seat of these most important metabolic changes. To-day we recognize the living cell as the place where the events occur with which the story of metabolism is concerned. The details of these events are still largely unknown and the minute mechanism of the tissue changes has only partly been disclosed. The role of enzymes in the chemical organization of the cell is, however, assuming an increased importance. In agreement with the views of Hofmeister the cell may be considered as a machine working with chemical and physico-chemical means. The microscope reveals a complexity of morphological structure which lends probability to the existence of equally diverse and intricate chemical powers. By way of illustration of this view we may recall the manifold capacities of the liver cells. In them a series of important physiological reactions are perfected. Glycogen is built up and deposited, or released, converted and discharged; bile pigments are elaborated from blood constituents; urea is synthesized; uric acid formed from precursors, or further oxidized; cholic acid constructed and united with glycocholic acid and taurin; phenols conjugated with sulphuric acid; toxic compounds chemically transformed, not to mention many less perfectly understood reactions.

It can no longer be doubted that ferments, or enzymes, are prominent in the chemical work of such cells; and, indeed, the liver tissue has been conspicuous in affording evidence of the presence of a large variety of soluble ferments acting under a diversity of conditions. Thus, a proteolytic enzyme is conspicuous in autolysis of the hepatic tissue; lipase, maltase, lacase, amidase, oxidase, as well as ferments which facilitate reactions with the purin compounds, are further specific examples of enzymes already recognized in this tissue. Whether, indeed, the essential chemical reactions of all tissue cells are facilitated by enzymes in the way which the investigation of the liver cells has made plausible, remains to be ascertained; but in any event it is very probable that enzymes of many kinds do exist in the different tissues and organs of the body, and, if so, they must be important factors in metabolic

changes. Further, recent investigations on the reversibility of enzyme action have placed fat and carbohydrate synthesis in a new light, and make the somewhat obscure anabolic processes and the redistribution of tissue constituents more susceptible of interpretation. These matters will be discussed in connection with the metabolism of the proximate principles themselves. Enough has been said, however, to indicate the possible function of enzymes in the intermediary processes of metabolism, and to point out some of the ways in which living cells may react. In the recognition of these facts a great step in advance has been made from the old view that oxygen is the immediate cause of all decomposition in the organism, as originally formulated by Lavoisier.

EXCHANGE OF MATERIALS; METHODS OF STUDY.

The study of metabolism has for its primary object, then, the investigation of the "exchange of materials" (*Stoffwechsel*)—the extent and character of the incessant transformations which accompany and determine the changes occurring within the living tissues. It aims to ascertain the conditions under which "the conversion of chemical tension into living energy" proceeds. In the past, various methods have been employed to furnish the data from which the physiology of metabolism can be understood. In the first place, the activities of the individual organs and tissues have been subjected to analysis in various ways. This method may yield fruitful results. For example, the blood supply to an organ may be regulated, the composition of the blood entering and leaving it may be accurately determined, and from the differences in chemical composition presented conclusions may be drawn in regard to the storing up, utilization, or destruction of the tissue components. Such methods have been applied with success to the investigation of the gaseous metabolism of different secretory structures such as the kidneys, pancreatic, and salivary glands. Quantitative measurements of the oxygen intake and carbon-dioxide output of the kidney during rest and diuresis, show that there is an increased consumption of oxygen during the increased secretory activity without any simultaneous corresponding removal of carbon dioxide (Barcroft and Brodie). During active secretion of pancreatic juice the consumption of oxygen by the pancreas is likewise increased (Barcroft and Starling). These examples indicate how perfusion of normal or "surviving" organs may facilitate the study of their metabolism. Changes of composition within the organs themselves may be ascertained by chemical analysis, and comparisons instituted between different tissues. In this way, much has been learned of the physiological and pathological role of the liver, as indicated by the relative abundance of characteristic carbohydrates and fats under varied conditions.

Altered functions of the body and changes in the chemical behavior of certain tissues after removal of specific organs are noted in many "extirpation" experiments. We need only refer to the alterations in the composition of blood and urine which follow the partial or complete exclusion of the liver from the circulation. Again, much has been learned, particularly in regard to synthetic and secretory processes, by

comparisons of the products of specific cells with the constituents of the blood and lymph surrounding them. In this way the metabolism of the mammary gland, for example, has been subjected to investigation, and the phenomena of milk production, as related to other nutritive changes or activities within the body, carefully studied. The comparison of the extent of chemical change during rest and activity in muscular and nervous tissues respectively has made it evident that the functions of these two types of physiologically active tissues are, quantitatively at least, not attended by similar metabolic changes. Corresponding studies in other cases, the salivary glands for example, have demonstrated that anabolism and katabolism may proceed simultaneously during activity, and the destruction of the cell substance during secretion be largely compensated for by a synthesis of new protoplasm (Y. Henderson).

A second method has long been employed with equal or greater success, namely, the study of the exchange of materials in the body as a whole. Indeed, it is this *total* exchange of the body which is more commonly referred to by the expression "metabolism." For many years it has been customary to investigate the metabolism of the organism as a unit, and to determine the influences of many factors upon it by ascertaining what materials have been utilized in the manifestation of the body-functions. The method is based essentially upon a recognition of the fact that certain chemical fragments of the body or its intake uniformly escape decomposition or oxidation within the organism, thereby constituting the true end-products of the chemical transformations normally occurring. A measure of the decomposition taking place is thus afforded by comparing the elements or substances which enter the body with those which leave it through various channels. We may therefore inquire more closely into the chemical nature of the intake and output, and consider what interpretation they allow regarding the processes of metabolism.

Intake.—The substances which compose the ingesta of man are found to be made up in large measure of the same groups of compounds which constitute the organs and tissues of the animal body. Broadly classified, they consist of inorganic and organic materials; the former are present in relatively small amounts, while the organic compounds are found to belong in great part to three distinct groups, *viz.*, carbohydrates, fats, and proteids. All examples of these groups contain the elements carbon, hydrogen, and oxygen; the proteids contain, in addition, nitrogen and sulphur; and phosphorus is further present, for example, in the nucleoproteids characteristic of all cellular food materials. Many other organic compounds enter into the composition of the intake. Some of them, like citric, malic and other acids, glucosides, ethereal oils, etc., are derived from vegetable sources; others accompany or are associated with the typical foodstuffs, and are exemplified in compounds like the creatin of meat, purin derivatives, alkaloids, amino-acids, and numerous others. The proportion of such substances contained in the ordinary diet is, however, very small in comparison with the three prominent groups or "proximate principles" mentioned. The former contain little potential energy and appear to be more important in relation to regulating or stimulating metabolic processes than in maintaining the material integrity of the body. This is equally true of the inorganic constituents of

the body's intake, represented by compounds of the elements sulphur, phosphorus, chlorine, potassium, sodium, magnesium, calcium, and iron, with traces of silicon, fluorine, and iodine. Perhaps water should be classed with these substances. They are for the most part highly oxidized compounds, and play only a subordinate part in the dynamic functions of the organism. However, they are none the less indispensable. The importance of calcium for the proper growth of bone, or of chlorides for the secretion of gastric juice, is obvious; yet too little consideration has been devoted in the past to the possible significance of many of these elements in metabolism and the perfect maintenance of the body's integrity.

If oxygen be added to these enumerated elements, the list of elements forming the intake will be essentially complete. A very small proportion leaves the body practically unchanged and without having entered into the metabolic processes at all. This is true not only of indigestible or undigested food residues which escape absorption and are rejected with the faeces, but also of compounds which are exempt from hydrolysis, cleavage or oxidation even in health, and find their way into the excretions slightly or totally unchanged. Many alkaloids behave in this way; compounds like caffeine or creatinin are eliminated in unaltered or only slightly altered form; and many foreign pigments reappear in their original make-up in the excreta.

Output.—The losses of the body are continually being manifested, and include all of the elements, the physiological role of which has already been discussed. They occur in the form of solid, liquid, and gaseous compounds, by far the greatest part of which represents typical end-products. A smaller portion of the output may include products of hydrolytic cleavage; and in addition to the relatively insignificant unaltered excreta mentioned above, a portion of the substances eliminated, such as hippuric acid, represents synthetic operations carried on within the body. Aside from the familiar paths of elimination—the lungs, skin, intestine, and kidneys—the body may experience slight losses in the removal of hair or other dead epidermal structures, the discharge of ova, the ejection of semen, in menstrual flow, or—what may become more important—in the secretion of milk. Under ordinary circumstances the latter losses are insignificant and negligible in any general account of the exchange of materials in the body. The gaseous products, leaving the body almost entirely by the lungs, are carbon dioxide and water. The kidneys eliminate the greater portion of the inorganic compounds and the nitrogenous excretory products, such as urea, creatinin, uric acid and other purin derivatives, hippuric acid, and ammonia (in combination), as well as large quantities of water; the latter, together with traces of the preceding compounds, escapes in perspiration from the skin; while the faeces contain secretions from the wall of the gut and the glands discharging into it, in addition to indigestible and undigested food masses which have never actually entered the organism itself. It may not be amiss to point out in this place that the physiological conception of the faeces has experienced considerable modification in recent years. It is now recognized that they may, under certain dietary conditions, represent to no inconsiderable extent materials actually metabolized, as well as the waste or “unutilized” residues of the ingesta.

Experimental investigations have also emphasized the importance of the intestine as a true excretory channel which may become even more important than the kidneys in the case of certain elements. Calcium and iron tend to leave the body in good measure through the stools in the form of phosphates, etc., as well as in the urine. To what extent the intestine may act as a compensatory organ of excretion in renal insufficiency remains to be learned. The relative importance of the various excretory channels may vary greatly according to external circumstances. Hammarsten has grouped the losses in an adult man in the following way: by *respiration*, about 32 per cent.; by *evaporation from the skin*, 17 per cent.; with the *urine*, 46 to 47 per cent.; and with the *feces*, 5 to 9 per cent.

Comparison of Intake and Output.—In the past, attention has been devoted almost exclusively to the elements carbon, hydrogen, and nitrogen; latterly, the quantitative occurrence of sulphur and phosphorus has begun to claim the recognition which it deserves. From the data obtained by analytical methods a comparison between certain features of the income and outgo of materials in the body under various conditions can be instituted. The *balance of matter* can thereby be determined, and the gain or loss to the body in the elements considered can be accurately ascertained. No evidence is needed to indicate that continued loss of any element without corresponding intake must inevitably lead to serious results. When a condition of perfect balance is reached the body is said to be in *nutritive equilibrium*. As an illustration of the establishment of this condition, with respect to both carbon and nitrogen in a man of 70 kilograms body-weight, the following table is offered:

BALANCE OF NUTRITION ON AN ADEQUATE DIET.

INCOME.			EXPENDITURE.		
Foods—Grams.	Nitrogen Grams.	Carbon Grams.	Excretions.	Nitrogen Grams.	Carbon Grams.
Proteid. 100	15.5	53	Urine.	14.4	6.16
Fat. 100	79	Fæces.	1.1	10.84
Carbohydrate. . . 250	93	Respiration (CO ₂)..	208.00
	15.5	225		15.5	225.00

Perfect equilibrium in respect to carbon and nitrogen is by no means always attained under normal conditions. The table on page 646 is selected to give some quantitative idea of the changes incidental to metabolic processes and the balance of matter in the case of three or four of the elements more commonly studied. The data are summarized from experiments by Atwater and Benedict on a young man of 76 kilograms body-weight.

Nitrogen Balance.—The balance of nitrogen demands special consideration, because this element is derived almost exclusively from a single group of the ingested materials—the proteids—in which it occurs to the extent of 15 to 18 per cent. Since all active tissues, as well as nearly all of the body fluids, contain proteid compounds in considerable

abundance, no marked metabolic changes ordinarily take place without an attendant katabolism or anabolism of proteid material. The disintegrated nitrogenous tissue constituents are eliminated almost exclusively

ESTIMATED INCOME AND OUTGO OF MATTER IN A MAN, AT REST AND ON ORDINARY DIET.—TOTAL AMOUNTS FOR FOUR DAYS.

Materials.	Weight.	Nitro- gen.	Carbon.	Hydro- gen.	Oxygen (esti- mated).	Ash.
<i>Income.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>
Water in food.....	3,687.6	412.6	3,275.0
Solids in food.....	1,892.4	64.2	944.4	139.3	695.5	49.0
Water of drink.....	4,000.0	447.6	3,552.4
Total.....	9,580.0	64.2	944.4	999.5	7,522.9	49.0
<i>Outgo.</i>						
Water in fæces.....	310.7	34.8	275.9
Solids in fæces.....	84.6	4.9	39.9	5.7	19.1	15.0
Water in urine.....	5,455.5	610.5	4,845.0
Solids in urine.....	227.9	63.4	47.2	11.9	80.5	24.9
Water of respiration, etc.....	3,524.0	394.3	3,129.7
CO ₂ of respiration, etc.....	3,248.3	886.0	2,362.3
Total.....	12,851.0	68.3	973.1	1,057.2	10,712.5	39.9
Outgo greater (+) or less (-) than income.....	+3,271.0	+4.1	+28.7	+57.7	+3,189.6	-9.1
<i>Body material.</i>						
Protein lost, estimated to furnish	- 25.6	-4.1	-13.6	- 1.8	- 5.9	- .2
Fat lost, estimated to furnish....	- 19.8	-15.1	- 2.3	- 2.4
Water lost, estimated to furnish....	- 479.0	-53.6	- 425.4
Ash constituents gained, fur- nished.....	+ 9.3	+9.3
Oxygen from air.....	2,755.9	2,755.9

through the kidneys, a smaller portion being excreted through the intestines. An estimation of the nitrogen-content of the output through these channels gives a measure of the extent of proteid katabolism occurring in the body. For it is now well established that no nitrogen is excreted in gaseous form by the lungs; and the amount of nitrogenous waste contained in the perspiration is practically negligible, except in cases of profuse sweating after muscular work, where over one gram of nitrogen per day has been estimated (Benedict). The balance of nitrogen can be ascertained with a high degree of accuracy, and with greater readiness than is the case for any other element.

In the condition described as nitrogenous equilibrium, it is assumed that the proteids of the tissues are neither increased nor diminished in amount; whereas when a deficit or gain of nitrogen is made evident by the balance-sheet, the tissues are supposed to lose or store up such compounds as the ordinary proteids or nucleoproteids. A gain or loss of carbon, without corresponding change in the nitrogen balance, may

affect the fat content of the body or the quantity of glycogen deposited. The peculiar significance of the nitrogen balance as an index to proteid changes in metabolism, is derived from the fact that the cellular activity constantly going on during life involves an incessant katabolism of the nitrogenous protoplasm. During hunger, there is an uninterrupted loss of nitrogen from the body. An organism can be kept in nutritive equilibrium on an exclusive but abundant diet of meat, consisting essentially of proteids. When, on the other hand, the proteid is replaced by an equally abundant intake of non-nitrogenous foods—fats and carbohydrates—a loss of nitrogen cannot be prevented. The tissue proteids are continuously disintegrated and their nitrogenous katabolites eliminated.

Although the animal body readily stores up carbon in the form of fat and glycogen, there is under ordinary conditions, *i. e.*, in healthy adults, no tendency to retain or construct proteid to a similar degree. When nitrogen in the form of proteids is taken into the organism in more than certain minimal quantities, the katabolism of the nitrogenous compounds is increased and the body attempts to establish a condition of nitrogenous equilibrium. Herein lies a further distinctive characteristic of proteid metabolism.

Balance of Sulphur and Phosphorus.—Up to the present time, relatively little attention has been given to the balance of other elements, notably sulphur and phosphorus, in metabolism. The data are obtainable in a similar way, but the conclusions are by no means equally clear and concordant. Both of these elements are eliminated, for the most part, in the form of highly oxidized compounds, through the kidneys and intestine. Volatile compounds, like hydrogen sulphide, are formed normally in traces only. Although very small quantities of simple sulphur compounds, like sulphates, are found in food and water, almost the entire intake of this element occurs in the form of proteid compounds containing from 0.3 to 2.4 per cent. of it. Within the proteid molecule the sulphur presumably exists in the complex represented by cystin. In the excretions it is found as inorganic or ethereal sulphates and in minor degree in the form of less highly oxidized compounds whose composition is at present unknown. Under normal conditions, metabolism and elimination of sulphur tend, as might be expected, to run parallel with that of nitrogen, although the variable content of sulphur in proteids renders a strict comparison impossible. Otherwise expressed, the ratio between nitrogen and sulphur is liable to vary with the kind of proteid substance disintegrated, the proportions in the latter varying all the way from 44 to 1 in oxyhæmoglobin to 5 to 1 in tendon mucin.

The role of phosphorus in the nutritive balance is even less certain than that of sulphur. Under ordinary conditions, the phosphorus intake is confined very largely to the phosphates of the food. Phosphorus occurs, however, in the phosphorized proteids, like the casein of milk and vitellin of the egg-yolk, as well as in the nucleoproteids and the complex fat lecithin, and, perhaps also, organic phosphorus compound of vegetable origin (like the salts of anhydro-oxyethylene disphosphoric acid). The body fluids and tissues abound in inorganic phosphates, which are especially conspicuous in the bones. The distribution of phosphorus in the important tissues of man has been estimated by Voit as follows: In nervous tissues, 12 grams; in the muscles, 130 grams; in

the bones, 1,400 grams. These figures indicate the degree to which the various parts may be expected to participate in the metabolism of phosphorus when either loss or retention of the element occurs. At one time it was assumed that the elimination of phosphorus might be taken as an index of changes in the nervous system. At present, however, physiologists are more inclined to associate disturbances in the phosphorus balance with changes in other tissues. In view of the presumably slight metabolic activity in the bones of adults during health, the elimination of phosphorus not directly attributable to phosphates ingested has lately more frequently been attributed to katabolism of the nucleoproteid constituents of the tissues. Since the active cells of the body everywhere contain the phosphorus-holding nucleoproteids, the possible significance of phosphorus elimination in its relation to cell katabolism cannot be overlooked. From the synthetic side, similarly, the question of the importance of phosphorus for the anabolism of cell protoplasm at once suggests itself. Phosphorus is excreted almost entirely in the form of phosphates of the alkalis and alkali earths, minimal quantities escaping in the form, perhaps, of glyceryl-phosphate.

The laws which govern the metabolism of phosphorus cannot yet be formulated with that certainty which applies to some of the other elements in the body, although the subject is now attracting the attention of numerous investigators. One of the most significant problems involves the relative importance of organic phosphorus compounds as contrasted with inorganic phosphates in the building up of new protoplasm. For example, are phosphorus-free proteids, like albumin or muscle myosin, fed with simple phosphates, capable of inducing a construction of the typical phosphorized cell constituents? And, if so, are such combinations equally as effective as the phosphoproteids, casein and vitellin? It is noteworthy that the food of the growing young in every case abounds in these phosphorus-containing proteids, whether it be in the milk or the egg-yolk. Moreover, more recent observations indicate that the organism retains phosphorus with greater readiness when it is exhibited in the organic form described above. Whether the more ready assimilation of organic phosphorus also applies to the phosphorized fats, like the lecithins (lecithans) remains to be demonstrated.

The differences in the behavior of the different types of phosphorus compounds in metabolism is well illustrated by the following balance-sheet for phosphorus and nitrogen, taken from experiments on a dog fed with the same quantities of these elements contained in the form of the phosphorized proteid casein, and the phosphorus-free proteid edestin and phosphates, respectively (from Zadik):

PERIOD.	NITROGEN.	PHOSPHORUS.	
I	+ 12.2	+ 0.45 }	Feeding with casein.
IV	+ 6.1	+ 0.34 }	
II	- 2.4	- 0.71 }	Feeding with edestin and phosphates.
III	+ 5.9	- 0.65 }	

The importance of such facts for the theory of nutrition, and in connection with some practical aspects of dietetics will be pointed out later. Enough has been said to make it clear that the balance of phosphorus in metabolism demands special interpretation. It appears, fur-

BALANCE OF INCOME AND OUTGO OF NITROGEN SULPHUR, AND PHOSPHORUS—AVERAGE PER DAY.

Experiment number.	Fuel value of diet per day.	NITROGEN.				SULPHUR.				PHOSPHORUS.			
		In food.	In faeces.	In urine.	Gain (+) or loss (-).	In food.	In faeces.	In urine.	Gain (+) or loss (-).	In food.	In faeces.	In urine.	Gain (+) or loss (-).
	Calories.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.
1.....	2908	15.82	0.74	14.31	+0.77	1.12	0.06	0.95	+0.11	2.29	0.78	1.41	+0.10
2.....	2901	15.82	.67	14.67	+.48	1.12	.06	.97	.09	2.29	.73	1.48	.08
3.....	2913	15.82	.70	14.16	+.96	1.12	.06	.93	.13	2.29	.78	1.42	.09
4.....	2082	12.05	.74	10.43	+.88	.94	.09	.72	.13	1.40	.44	1.03	.07
5.....	2607	18.52	.87	16.50	+1.15	1.44	.08	1.12	.24	3.07	1.10	1.74	.23
6.....	1555	9.76	.27	10.94	-1.45	.69	.02	1.75	.08	1.60	.37	1.12	.11
7.....	1660	10.11	.45	11.51	-1.85	.70	.04	.83	.17	1.58	.60	1.00	.02
8.....	3336	20.22	1.04	15.52	+3.65	1.40	.09	1.06	.25	3.16	1.42	1.49	.25
9.....	1656	10.11	.43	12.87	-3.19	1.70	.04	1.88	.22	1.58	.50	1.32	.24
10.....	3329	20.70	1.05	16.58	+3.07	1.36	.10	1.21	.05	3.26	1.37	1.49	.40

thermore, as if there is far less tendency toward equalization between intake and output than has been found so conspicuous in the case of nitrogen and sulphur. Otherwise expressed, the organism is capable of storing up (synthetically or otherwise) comparatively large quantities of phosphorus during longer periods of time, and this without close relation to simultaneous changes in the metabolism of nitrogen. All the foregoing facts must be taken into consideration, before any wide-reaching attempt is made to connect the excretion of phosphates with the katabolism of any specific phosphorus-containing constituents of the body, like the nucleoproteids, osseous, or nervous tissues.

The table on page 649, containing data taken from experiments on a single individual, will give some idea of the relations actually pertaining in man under average conditions (Sherman).

In general, the metabolism and balance of sulphur will be found to run approximately parallel with that of nitrogen. With phosphorus the parallelism is less apparent; and in no case is the gain or loss here great enough to justify calculations of the materials stored or broken down. Finally, the relatively large proportion of phosphorus leaving the body in the feces is here referred to in illustration of what we have already stated regarding the importance of the intestine as an excretory channel for some compounds.

METABOLISM OF ENERGY.

The consideration of metabolism in which we have been engaged up to this point suggests some idea of the transformations in the functional activities of the organism, and we have gained some conception of the character of the chemical reactions thereby involved. A more intimate study of the topics outlined would afford a clearer understanding of the workings of the individual organs and tissues, as well as of the body as a whole; and with the development of physiological chemistry, we may confidently hope to gain a deeper insight into the chemical changes which underlie metabolism, and to formulate more definitely the laws which govern these processes. There are, however, quite different and equally important aspects of metabolism which deserve careful study. The simple comparison of the income and outgo of matter, or the investigation of the synthesis or combustion of proteid, fat, and carbohydrate in the body leaves many of the problems of nutrition completely unsolved. They merely afford incomplete data from which to estimate the actual needs of the body for its work or to determine the relative nutritive value of the different types of ingesta under varying conditions. When, however, it is remembered that the *chemical transformations of the body are accompanied by physical phenomena* and that the exchange of materials goes hand in hand with a *transformation of energy*, the study of metabolism presents a new and broader aspect. We are thus prepared to take a new view of the organism as a mechanism in which, incidental to the life-processes, potential energy becomes kinetic. The chemical energy latent in the food and body materials is liberated by oxidation or cleavage in the form of work and heat. It must now be apparent that food has two functions in the body, namely, the building, or repair, of

tissues and the yielding of energy. The uses of the food and its service to the organism are thus extended beyond the conception which the consideration of transformation of materials alone has suggested. *Metabolism implies a transformation of energy as well as an exchange of materials.*

It is in connection with the chemical changes in metabolism that the transformation of energy from a potential to a kinetic form takes place; and precisely as the nature of the former (the chemical changes) is imperfectly understood, so the physical changes require more extensive investigation in anticipation of a complete interpretation of how they occur. The oxidative, or combustion processes are unquestionably the most important ones, although undoubtedly potential energy also becomes kinetic in the cleavage of complex compounds to simpler ones. But the physiological energy transformations correspond with the chemical processes of metabolism in being more complex apparently, than is the case in combustion outside of the body, and also more gradual. In general the end-products of combustion within the organism are the same as those obtained by burning the compounds in oxygen; and there is every reason to believe that the quantity of potential energy transformed in the combustion of any substance within the body will be the same as that noted by the usual physical measurement in the laboratory.

Without disclosing the ultimate nature of life itself, experience has shown that the animal organism does not have the capacity to create or destroy energy. The manifestations of life are, however, accompanied by the *transformation* of energy. This energy is obtained with the food, in the form of chemical compounds; it is in the manifold transformations of the latter that heat production, body work, and electrical phenomena have their origin. The energy so liberated in the body and its organs manifests itself continually in such ways as the beating of the heart, the respiratory movements, peristaltic movements, circulatory phenomena, osmotic exchanges, etc., ultimately being lost to the body in external work, heat, or water vapor. A very small part escapes in the organic constituents of the urine and fæces.

It is therefore quite plain that just as the cells require certain *materials* to replace the waste and disintegration going on within them, they also need the *energy* which they derive from the contributions brought to them by the circulating fluids of the body or stored up within themselves. The demands for energy may, however, be satisfied in more diverse ways than is the case with the demand for materials. For while there are certain compounds, like the proteids, which, owing to their peculiar composition, are always essential for the maintenance of cellular life, we shall see that the body can satisfy its energy-yielding requirements from a variety of sources with equal readiness. The metabolism of matter accordingly is characterized by certain *qualitative* features; that is, under determined conditions definite kinds of compounds must be available if the functions are not to suffer deterioration. In the metabolism of energy, on the other hand, *quantitative* relations play the important part. The potential energy must be renewed and adequate provision made for the maintenance of body temperature and activity. This means that proper quantities of nutrients must be furnished, without

emphasizing the type of compound in which the energy is stored. The fact that in man and many other organisms energy is liberated by cleavage with intermediation of respired oxygen has, as Rubner pointed out, a distinct advantage; for *oxidative* cleavages render latent energy available in greater proportion than many other forms of decomposition. Thus, the heat afforded in such living processes as alcoholic fermentation or lactic acid fermentation is comparatively slight. And if the ferment organisms involved in them regulate their food supply in correspondence with the proportion of energy set free in the decompositions which they incite, it becomes apparent why they afford so large a yield of fermentation products.

Methods of Study.—Since the organic foodstuffs contain a store of potential energy which may become transformed sooner or later in metabolism, we may take this energy as a measure of their “fuel value,” that is, their value in accomplishing work and forming heat when they are metabolized in the body. The quantity of heat set free when a given organic food compound is burned with oxygen in a calorimeter is an equivalent and measure of its potential energy. We may, therefore, appropriately estimate the fuel value of a nutrient substance by its heat of combustion. And inasmuch as the greater portion of the energy changes in the body result in the liberation of heat, it has become customary to measure these transformations by similar heat units. The “heat of combustion” of a substance is expressed in large calories or kilogram-degree units of heat, and in small calories, *i. e.*, gram-degree units of heat. The former represent the quantity of heat required to raise 1 kilogram of water 1° C.; the small calorie represents the heat required similarly to raise the temperature of 1 gram of water. Therefore, 1,000 small calories = 1 large calorie.

In the calorimeter, substances are burned up in an atmosphere of oxygen; as is the case in the body, fats and carbohydrates are decomposed to carbon dioxide and water. Proteids yield nitrogen, sulphuric (and sometimes phosphoric) acid, in addition to carbon dioxide and water. In metabolism the combustion of proteids is less complete. The nitrogenous moiety of the molecule is eliminated in the form of less simple bodies in the urine and faeces. We have, accordingly, to distinguish between their physiological fuel value and that determined by direct measurement in the calorimeter. This physiological fuel value of the proteids can be ascertained by subtracting from the fuel values of the total material, the heat of combustion of the incompletely oxidized excretory products—such as the urea, uric acid, creatinin, etc., of the urine—and the unutilized nitrogenous residues of the food excreted by the intestine, corresponding to the proteid considered. That is to say, “If we subtract the potential energy of these products from that of the total material from which they are formed, the difference will be the amount of energy which has been liberated in their consumption in the body.” The loss of energy represented by the normal incomplete combustion of the proteids may amount to 22 to 28 per cent. (Rubner).¹ Finally, it may be added that when a portion of the intake is anabolized

¹Tigerstedt has noted as a general rule that the percentage loss of calories in the faeces is roughly equal to the figure obtained by estimating the percentage relation of the dry solids of the faeces to the total dry solids of the food ingested.

or stored in the body, its potential energy is likewise held in reserve; and when katabolism of the tissues proceeds uncompensated from without, the metabolism of energy is proportionate to the yields required of the particular compound (proteid, fat, glycogen), which is burned or split up, with due allowance for the corrections suggested above.

The calorimetric researches of Berthelot, Stohmann, Rubner, Atwater, and their associates have given us a large number of data relative to the potential energy or fuel value of many compounds. Relatively few figures apply to the isolated foodstuffs—the proteids, fats, and carbohydrates. A few typical examples are given below:

HEATS OF COMBUSTION OF ORGANIC SUBSTANCES.

—per gram—

<i>Proteids.</i>	<i>Calories.</i>	<i>Fats.</i>	<i>Calories.</i>	<i>Carbohydrates.</i>	<i>Calories.</i>	<i>Other organic substances.</i>	<i>Calories.</i>
Beef.....	5.65	Beef fat.....	9.50	Pentoses.....	4.00	Urea.....	2.52
Protein of meat..	5.65	Mutton fat	9.51	Dextrose.....	3.75	Alcohol.....	7.07
Egg albumin.....	5.71	Lard.....	9.59	Cane sugar.....	3.96	Citric acid.....	2.39
Casein of milk	5.78	Butter fat.....	9.27	Milk sugar.....	3.86	Creatin.....	4.27
Gluten of wheat...	5.95	Olive oil.....	9.47	Starch.....	4.20	Uric acid.....	2.62
Gelatin.....	5.27	Fat of cereals..	9.30	Dextrin.....	4.11	Leucin.....	6.53
Vegetable proteid	5.00			Glycogen.....	4.19	Fæces (average)	6.20

It need scarcely be pointed out that such figures, by themselves, give little idea of the actual fuel value or available energy attributable to the nutrient substances as they are ordinarily consumed. The diet of man consists of foods of complex composition, rather than definite chemical compounds; and it is only under experimental conditions that the pure foodstuffs enter into consideration. The actual amount of energy which the body can derive from a given diet depends upon a variety of factors, chief among which are the quantities and chemical energy of the foodstuffs *available* and the amount of incompletely oxidized material rejected in the excretions.

Availability of Nutrients.—We may digress here to discuss what is meant by the expression “available foodstuffs” or “available nutrients.” If the ingesta were *completely* digested, absorbed, and utilized, such distinctions would be unnecessary. But the ordinary make-up of the diet is such that the nutrient materials are in part either undigested or indigestible, and thus represent a loss to the body in relation to the energy-yielding compounds ingested. Strictly speaking, the excreta from the alimentary tract represent *both* residues of metabolic products and undigested food residues. Atwater has suggested the term “co-efficient of digestibility” to represent the factor found by subtracting the undigested residues from the food. The “co-efficients of availability” are found by subtracting the total excreta from the total food. Commonly, the expressions digestibility and availability are used synonymously in reference to the foodstuffs, owing to the practical difficulty of distinguishing between unutilized food residues and true metabolic products in the fæces. From experiments made in many laboratories, data have been collected in the course of an inquiry regarding the nutrition of man, carried out under authority of the United States government, and co-efficients have been obtained for different classes of materials. From the data thus observed, factors were assumed for the total food of ordinary mixed diet, and the results of over 400 such experiments have been collated and the

co-efficients of availability of the foodstuffs calculated. The proposed co-efficients represent very nearly the actual average availability (or digestibility) of the nutrients of ordinary mixed diet, as will be seen in the appended table (Atwater):

AVAILABILITY OF NUTRIENTS.

	<i>Protein.</i>	<i>Fats.</i>	<i>Carbohydrates</i>
Proposed factors.....	92.0 per cent.	95.0 per cent.	97.0 per cent.
Factors found in average of 411 experiments.....	91.1 per cent.	94.8 per cent.	96.8 per cent.

In the developing infant, Rubner and Heubner have found a utilization of 91 to 94 per cent. of the total nutrients under normal nutritive conditions.

It is important to bear in mind the essential fact brought out by these figures, namely, that only a *portion* of the materials ingested is actually made available or utilized in metabolism. The *available energy* of the fats and carbohydrates is the total energy of their available material. In the case of the proteids, however, the digested and absorbed material is not completely broken down and oxidized; the *available energy* of this group is therefore represented by the difference between the total and that of the excreta which escape unoxidized. Such general statements as these are of course subject to minor modifications, the discussion of which would be unprofitable in this place. The table on page 655 illustrates the differences between the physical and physiological fuel value (Physiologischer Nutzeffekt) of the chief components of an ordinary diet.

Twenty years ago Rubner proposed a series of factors by means of which the energy-yielding value of the foodstuffs could be calculated, namely:

1 gram of proteid yields	4.1 Calories (large).
1 gram of fat.....	9.3 Calories.
1 gram of carbohydrate.....	4.1 Calories.

Since that time the heat of combustion of a large number of compounds has been determined, the proportions of the foodstuffs in the ordinary foods of man have been ascertained on an extensive scale, and many digestion and absorption experiments have been added to the literature. From the data secured by a careful review and compilation of the statistics thereby furnished, Atwater and his associates have proposed a slightly altered series of factors, as shown on page 655.

Outside of the three groups included above, few other food materials have any significant interest. Alcohol and a few compounds of the fatty acid series, such as asparagin, may enter into the diet at times; but the other organic substances need not receive serious consideration as sources of energy or matter for the organism. Some of them, to be sure, liberate energy as heat when they are burned with oxygen in the calorimeter. In the body, however, they cannot serve as sources of energy, because they are either not absorbed or fail to be katabolized. To this group belong the inorganic salts and water, which furnish no energy to the organism, however indispensable they may be for the performance of its functions. An engine requires lubricants even though it draws its supply of energy from coal.

FACTORS FOR HEATS OF COMBUSTION AND FUEL VALUES OF NUTRIENTS IN DIFFERENT GROUPS OF FOOD MATERIALS AND IN MIXED DIET. (ATWATER.)

Kind of Food Material.	Nutrients furnished by each group per 100 grams total.	Heat of combustion per gram.	Proportion of total nutrients actually available.	Total energy per gram in available nutrients.	Fuel Value.	
					Per gram available nutrients.	Per gram total nutrients.
	A	B	C	D = B × C	E ₁	F ₂
<i>Protein.</i>	<i>Grams.</i>	<i>Calories.</i>	<i>Per Cent.</i>	<i>Calories.</i>	<i>Calories.</i>	<i>Calories.</i>
Meats, fish, etc.....	43.0	5.65	97	5.50	4.40	4.25
Eggs.....	6.0	5.75	97	5.60	4.50	4.35
Dairy products.....	12.0	5.65	97	5.50	4.40	4.25
Animal food.....	61.0	5.65	97	5.50	4.40	4.25
Cereals.....	31.0	5.80	85	4.95	4.55	3.70
Legumes.....	2.0	5.70	78	4.45	4.45	3.20
Vegetables.....	5.5	5.00	83	4.15	3.75	2.90
Fruits.....	0.5	5.20	85	4.40	3.95	3.15
Vegetable food...	39.0	5.65	85	4.80	4.40	3.55
Total food.....	100.0	5.65	92	5.20	4.40	4.00
<i>Fat.</i>						
Meat and eggs.....	60.0	9.50	95	9.00	9.50	9.00
Dairy products.....	32.0	9.25	95	8.80	9.25	8.80
Animal food.....	92.0	9.40	95	8.95	9.40	8.95
Vegetable food...	8.0	9.30	90	8.35	9.30	8.35
Total food.....	100.0	9.40	95	8.90	9.40	8.90
<i>Carbohydrates.</i>						
Animal food.....	5.0	3.90	98	3.80	3.90	3.80
Cereals.....	55.0	4.20	98	4.10	4.20	4.10
Legumes.....	1.0	4.20	97	4.05	4.20	4.05
Vegetables.....	13.0	4.20	95	4.00	4.20	4.00
Fruits.....	5.0	4.00	90	3.60	4.00	3.60
Sugars.....	21.0	3.95	98	3.85	3.95	3.85
Vegetable food...	95.0	4.15	97	4.00	4.15	4.00
Total food.....	100.0	4.15	97	4.00	4.15	4.00

Kind of material.	Heat of combustion per gram.	Avail-ability.	Fuel Value.			
			Referred to available nutrients.		Referred to total nutrients.	
			per gram	per pound	per gram	per pound
	<i>Calories (large).</i>	<i>Per Cent.</i>	<i>Calories (large).</i>	<i>Calories (large).</i>	<i>Calories (large).</i>	<i>Calories (large).</i>
Protein.....	5.65	92	4.4	2000	4.0	1820
Fats.....	9.40	95	9.4	4260	8.9	4040
Carbohydrates.....	4.10	97	4.1	1860	4.0	1820

¹ Values for fats and carbohydrates, same as corresponding values in column B. Values for protein, same as corresponding values in column B minus 1.25.

² Values for fats and carbohydrates, same as corresponding values in column D. Values for protein, same as corresponding values in column D minus 1.25.

From the tables presented above, it is apparent that proteids and carbohydrates furnish practically the same yield of energy in metabolism, in contrast with the fats which afford far more heat per unit of material. If the composition of the ingesta, with reference to the content of proteids, carbohydrates, and fats is known, the fuel value of the mixed food materials can readily be calculated, and approximate corrections made for the availability of the different constituents. Let us say, for example, that an individual consumes 100 grams of proteid, 400 grams of carbohydrate and 100 grams of fat. The fuel value of the intake, expressed in large calories is as follows:

$$\begin{array}{rcl}
 100 \text{ grams of proteid} & \times 4.4 = & 440 \text{ Calories.} \\
 400 \text{ grams of carbohydrate} & \times 4.1 = & 1,640 \\
 100 \text{ grams of fat} & \times 9.4 = & 940 \\
 & & \hline
 & & 3,020 \text{ Calories.}
 \end{array}$$

During the past few years our knowledge of the chemical composition of food materials has been added to largely, through the efforts of the United States Department of Agriculture. Quantitative data regarding the make-up of a large number of products have been compiled from over 4,000 analyses of American food materials alone, and in many instances the fuel value has been determined directly with the calorimeter. Such statistics have become of great service in the practical study of dietetics.

With this introduction to the consideration of the transformation of energy in the living body and with the foregoing brief reference to terms employed, we may proceed to consider some of its phenomena and the laws which govern them in their application to metabolism. No adequate treatment is possible without a thorough understanding of the principle of the conservation of energy. A knowledge of the physical relations which this involves may be assumed to be familiar. The circulation of energy is intimately associated with the circulation of the elements in the living body as well as in the inorganic world about us. If it is as impossible to destroy energy as it is to destroy matter, we must expect, when the chemical potential energy of the food or the body tissues is used up, to find an equivalent amount of other forms of energy appearing in the body. Energy itself cannot be directly observed and pursued; but we can measure it by its manifestations of motion, whether it be a visible motion of masses of matter or that invisible motion of infinitely smaller particles which is spoken of as heat.

In accordance with this statement, it is to be noted that the body is continually *producing heat*, and furthermore it is engaged in movement and *performing work*. These are the essential manifestations of a transformation of energy. It has frequently been suggested that in the performance of *psychical functions* also, chemical potential energy must be liberated. We are, however, unable to say definitely whether the phenomena of consciousness follow the law of the conservation of energy. As Bunge has well expressed it: "There is probably, in the afferent and central organs, a chain of processes intervening between stimulation and sensations, as there is between will and muscular action. We are quite unable to decide whether the last form of motion, which reaches the brain

as the result of stimulation, is converted into sensation, or only serves as an impulse originating sensation, possibly from chemical potential energy. It is conceivable that an entirely new and particular kind of causal connection may be at work in this case.

"People have tried to prove experimentally that intellectual exertion has an influence on metabolism, as shown by the amount of excretions. All these experiments fail on account of the impossibility of measuring intellectual exertion, or of even deciding whether it was greater or less. A man who shuts himself up in a dark room, with the intention of keeping his mind a blank, may involuntarily exercise it more than if he were to sit down to his books with the intention of exerting all his intellectual faculties; besides, we ought to take into consideration the emotions, which probably exceed all mental exertions in the expenditure of energy, and which we cannot call into play or dismiss at will.

"We must consider moreover that the weight of the brain is less than two per cent. of the weight of the body, and that only a portion of the brain is employed in mental functions. Even if the metabolism of this organ were, by higher psychical activity, promoted to the utmost, we could not expect to recognize this fact in an increase in the total metabolism. Even if it could be distinguished, we should not be justified in concluding that the work of the mind was converted potential energy. The conversion might be an indirect one."

Finally, there is no evidence in man and the higher animals that energy is liberated in the form of light or electricity, as in some of the lower forms of life. At any rate, if such transformations do occur, the energy must finally leave the body as heat, or in some form which we do not at present recognize.

Balance of Energy.—As the body receives its energy supply solely in the form of chemical compounds, it should be possible to determine experimentally the *balance of energy* in the organism, provided that the physical and chemical changes taking place occur in obedience to the laws of the conservation of energy and matter. The essential data for comparison are, obviously, the income and outgo of energy. The former of these quantities, the income, can be estimated in terms of calories or heat units after corrections have been made for the loss of potential energy in the corresponding incompletely burned metabolic end-products. When the tissue constituents themselves furnish the energy liberated, the quantitative relations can be established by ascertaining the exchange of materials which has ensued; and thus the energy of the katabolized compounds can be calculated.

In the measurement of the *output of energy* from the body, the quantities to be ascertained are the heat given off from the body and the external muscular work, which can in turn be converted into terms of heat units. The muscular work of the internal organs is transformed into heat before it leaves the body. Briefly reviewed, the factors to be determined in preparing the balance-sheet of the income and outgo of energy are: (1) Potential energy of the organic compounds of food and drink; (2) potential energy of organic compounds of fæces, urine, and products of perspiration and respiration; kinetic energy given off as heat and external muscular work (and other possible forms).

Since the study of the balance of matter gives the data from which the gain or loss of proteid, fat, and carbohydrate in the body can be estimated, a calculation of the fuel value of the corresponding foodstuffs can readily be made. Furthermore, the potential energy of the ingesta can be determined directly by calorimetric methods. Thus the conditions are given for comparing the energy available in metabolized materials with the quantity of heat generated by the body. Various devices have also been perfected by which the external muscular work of the organism can be converted into heat within the respiration calorimeter and thus all the energy transformed (whether as heat or work) determined in heat units. Rubner was the first to show, by calorimetric studies on animals, that the quantity of heat given off by the body is almost exactly equivalent to that calculated from the available potential energy of the foodstuffs actually metabolized, under various conditions of diet. Figures from his experiments are quoted below:

Character of diet.	Number of days.	Heat units calculated.	Heat units found.	Percentage difference.
No Food.	{ 5 2	1,296.3 1,091.2	1,305.2 1,056.6	} - 1.42
FAT	2	1,510.1	1,495.3	- 0.97
MEAT AND FAT	{ 8 12	2,492.4 3,985.4	2,488.0 3,958.4	} - 0.42
MEAT	{ 6 7	2,249.8 4,780.8	2,276.9 4,769.3	} + 0.43

Laulanie has likewise found a correspondence between the calculated chemical energy of the compounds metabolized and the heat given off in the case of small animals during rest. These experiments demonstrate almost beyond doubt that the life of the higher animals is essentially a process of combustion and that the law of the conservation of energy is strictly applicable to the living body. The latter controls no permanent sources of energy other than those furnished by the food. More recently the demonstration of this fundamental principle has been furnished in the case of man under various conditions of rest and activity, by Atwater and his associates in this country. The results of 45 experiments covering one hundred and forty-three experimental days are summarized in the table on page 659 (Atwater and Benedict).

The remarkable average agreement between the theoretical and actual changes of energy in the human body evidenced by these figures, indicates that the law of the conservation of energy obtains here precisely as *à priori* considerations would lead us to expect. The actions of the organism are thereby shown to be clearly within the domain of ordinary physical and chemical laws. It is evident, also, that in the study of metabolism, the calorimetric method is capable of furnishing data quite comparable in value with the facts learned by study of the purely chemical changes. We are enabled to ascertain the energy transformations which go on.

COMPARISON OF INCOME AND OUTGO OF ENERGY IN 45 METABOLISM EXPERIMENTS COVERING 143 EXPERIMENTAL DAYS—AVERAGE AMOUNTS PER DAY.

Subject and Kind of Experiment.	D u r a t i o n .	Net income (potential energy of material oxidized in the body).	Net outgo (k i n e t i c energy given off from the body).	Difference (in terms of net income).	
<i>Ordinary diet.</i>					
REST EXPERIMENTS.	<i>Days.</i>	<i>Calories.</i>	<i>Calories.</i>	<i>Calories.</i>	<i>Per cent.</i>
7 Experiments with E. O.	25	2,268	2,259	- 9	-0.4
1 Experiment with A. W. S.	3	2,304	2,279	- 25	-1.1
3 Experiments with J. E. S.	9	2,118	2,136	+18	+0.8
1 Experiment with J. C. W.	4	2,357	2,397	+40	+1.7
Average of 12 experiments with E. O., A. W. S., J. F. S., and J. C. W.	41	2,246	2,246	0	0.0
WORK EXPERIMENTS.					
2 Experiments with E. O.	8	3,865	3,829	- 36	-0.9
4 Experiments with J. F. S.	12	3,539	3,540	+ 1	0.0
14 Experiments with J. C. W.	46	5,120	5,120	0	0.0
Average of 20 experiments with E. O., J. F. S., and J. C. W.	66	4,682	4,676	- 6	-0.1
Average of all rest and work experi- ments (32) with ordinary diet.	107	3,748	3,745	- 3	-0.1
<i>Special diet.</i>					
REST EXPERIMENTS.					
6 Experiments with E. O.	17	2,313	2,319	+ 6	+0.3
3 Experiments with A. W. S.	6	2,308	2,356	+48	+2.1
1 Experiment with J. F. S.	3	2,124	2,123	- 1	0.0
Average of 10 experiments with E. O., A. W. S., and J. F. S.	26	2,290	2,305	+15	+0.7
WORK EXPERIMENTS.					
1 Experiment with E. O.	4	3,922	3,928	+ 6	+0.2
2 Experiments with J. F. S.	6	3,583	3,552	-31	-0.9
Average of 3 experiments with E. O., and J. F. S.	10	3,719	3,702	-17	-0.5
Average of all rest and work experi- ments (13) with special diet.	36	2,687	2,695	+ 8	+0.3
Average of all rest and work experi- ments (45) all diets.	143	3,481	3,481	0	0.0

It is instructive to examine the relative participation of different paths in the discharge of energy from the body. The significant features are plainly indicated in the summary on page 660, prepared from the experiments of Atwater and Benedict.

The important role of the body surfaces in the dissipation of heat is thus made apparent.

Replacement of Nutrients.—The conception of metabolism as a process in which the body transforms the potential energy of the food in accord with well-known physical and chemical laws, suggests the pos-

PERCENTAGE OF ENERGY GIVEN OFF FROM THE BODY IN DIFFERENT WAYS.

PATH OF HEAT ELIMINATION	Rest, fasting.	Rest, with food.	Work experiments.
By radiation and conduction.....	73.4	74.4	71.4
In urine and faeces.....	0.9	1.4	0.6
In water vaporized from lungs and skin.....	25.7	24.2	18.4
Heat equivalent of external muscular work done.....	9.6
	100.0	100.0	100.0

sibility that different substances might replace one another, as nutrient materials, in proportion to their energy-yielding or fuel value. This would mean that these different materials are of service to the organism in proportion to the heat and work which they can develop, despite any differences in the chemical transformations by which they are metabolized. From this point of view, the content of energy (as expressed in the available heat of combustion) becomes the crucial factor in estimating the importance of any food; the demands of nutrition are satisfied by supplying energy to the body. Limitations to such a conception at once arise, as, for example, the impossibility of maintaining life unless at least a minimum of proteid is furnished to make good the continued degradation of the nitrogenous tissues. Yet the general idea that the foodstuffs can replace one another to a very large, if not an unlimited, extent in metabolism was long ago suggested. In 1883, Rubner published experimental observations, which were later widely extended, indicating that the organic nutrients can under certain conditions replace each other in proportion to the energy which they furnish outside of the body, corrections being made for the availability and unoxidized fragments of the typical nutrients. In Rubner's earlier experiments, the actual quantities of various substances which yielded the same amount of heat as 100 grams of fat were determined in animal calorimetric trials and compared with the figures derived in a previous chapter for the heat values of compounds as deduced and corrected from physical measurements, *viz.*:

1 gram of protein.....	= 4.1 large calories.
1 gram of fat.....	= 9.3 large calories.
1 gram of carbohydrate ..	= 4.1 large calories.

The relatively close correspondence of the observed and calculated values is shown in the table on page 661.

With the exception of the slight differences in the case of the proteids, these experiments show a satisfactory equivalence between the actual heat production and the computed values. From this we may conclude not only that the foodstuffs yield heat in the body in proportion to their estimated fuel value, but that the nutrients may replace each other in proportions corresponding to their heat value. By the latter is of course here understood their "available" or "physiological" heat value—"metabolizable energy," as expressed by Armsby. The quantities which

EQUIVALENT TO 100 GRAMS OF FAT. (RUBNER.)

SUBSTANCE.	Found in animal experiments.	Computed from available energy.	Differences.
	Grams.	Grams.	Per Cent.
Muscle proteid.....	225	213	+ 5.6
Muscle tissue.....	243	235	+ 4.3
Starch.....	232	229	+ 1.3
Cane sugar.....	234	235	0
Grape sugar.....	256	255	0

thus replace each other are said to be *isodynamic*. Accordingly, it follows that the bodies of the higher animals do not require the same quantities of different foods for the purposes of metabolism; but they obey a law of *isodynamic replacement* according to which the foodstuffs may be substituted for one another in inverse proportion to their available energy.

These observations and deductions which place food values in a new light and emphasize the energetics of metabolism so strikingly, have received wide acceptance. Renewed investigation has, however, demonstrated that the foodstuffs are strictly isodynamic only within certain narrow limits and under definite conditions. The animal body is by no means a machine so simple that it transforms energy with such indifference toward the *kinds* of materials metabolized. Whenever transformations go on, the yield of heat is strictly proportional to the energy-content of the materials metabolized; but the regulation of the kind of food or body constituents burned up is apparently far more complex than was formerly assumed. A slight departure from theoretical conditions has already been noted incidentally in the case of the proteids. Rubner has, indeed, gradually modified his earlier conception of the isodynamic replacement of the foods to apply strictly only to small amounts of the latter under conditions approaching the maintenance ration, *i. e.*, conditions of nutritive equilibrium. With these reservations the general idea expressed above still forms an important part of the current theories of nutrition, and is capable of at least partial demonstration. The chief practical value of the law of isodynamic values lies in the application of the idea that food is a source of energy, and in the interpretation of the relative significance of different diets.

We cannot undertake here to review in detail the criticism and changes which the preceding ideas have experienced since they were first promulgated. A difference between the effects of small and large amounts of food was early discovered. Moreover, the work of digestion and assimilation varies widely with different types of food, and introduces a new source of heat. In some cases the heat thus produced is utilized to warm the body, and less energy is withdrawn from that stored in the tissues. At other times, however, the excess of heat arising from the work of digestion cannot thus be compensated for. Furthermore, environmental conditions as well as feeding play a role in the adjustment. In a general way it may be pointed out that materials containing the same amount of total energy may require the expenditure of very unequal amounts of energy for their digestion and utilization; and although the general laws of energy

naturally support the theory of isodynamic replacement, the discrepancies largely hinge upon the factors which determine the net *available* energy in each case. The facts may also be expressed by saying that when large, but isodynamic, quantities of different foodstuffs are compared, they exert unequal energy transformations. Proteids are especially peculiar in this respect, in stimulating heat production. Without attributing it specially to the work of the digestive or other glands, Rubner has lately applied to this function the expression *specific dynamic action*. The isodynamic values of fats and carbohydrates show a tendency to be maintained; but when the proteids are exhibited in excess they exert a specific dynamic action in provoking a disproportionate transformation of energy with liberation of heat. A further example of an apparently similar specific action is seen when alcohol is administered. The possibility of its combustion and an isodynamic replacement of ordinary nutrients seems to depend upon conditions which involve both the individual and the quantities administered. "In the transformation of energy, there is, in addition to the diet, a quite different factor which is of potent influence, namely, the condition of the body and its dependence on the thermal environment. . . . Amid a diversity of conditions of life and nature we are too prone to regard the body as something fixed (*Einheit*); whereas in fact, when the conditions about and within us are considered, it is an extremely changeable organism." Accordingly, when we consider the needs of the body from the standpoint of the changes of energy going on within it, too much emphasis must not be placed upon absolute figures or fixed proportions. Despite the tendency toward isodynamic utilization of materials, thermal conditions, individuality, age, etc., in addition to the relative quantities of different nutrients offered, must be reckoned with. As elsewhere in physiology, so in the study of metabolism, adaptation processes are met with. The specific-dynamic action of proteids, in inaugurating a liberation of energy far greater than the small plus of digestive work entailed by them can account for, applies broadly only to the adult. In the young and growing organism, a different disposition of proteids is made. We are dealing, in the case of the animal body, with a complicated apparatus the workings of which cannot be expressed in simple laws.

Mechanical Efficiency of the Body.—Before leaving the consideration of the body as an energy-transforming mechanism, we may refer to its efficiency and capacity for work. Part of the energy stored within the organism is expended in maintaining physiological functions and in the case of the heart the work done can readily be calculated. The energy involved in these processes is, however, ultimately transformed into heat, in which form it leaves the body. In speaking of the working capacity of the body we ordinarily refer to external muscular work. It is a familiar fact that in the performance of an ordinary steam-engine a relatively small fraction of the energy furnished in the form of fuel can be transformed into mechanical energy, the greater portion being dissipated as heat. The average efficiency of such engines, that is, the proportion of the expended energy which appears as work done, is under 15 per cent. The determination of this ratio in man is attended with considerable difficulty. The necessary data are derived by comparing the excess of energy transformed when work is done with the heat equivalent of the external muscular work done. The latter can be measured on such

apparatus as an ergometer, while the entire excess of energy katabolized for working purposes can be ascertained through comparison between the energy metabolism in days of rest and (measured) activity in the same individual. Experiments by Atwater and Benedict, on a bicycle rider, gave 19.6 as the efficiency percentage.

Other experiments in which the necessary data have been accurately determined have given efficiency figures of a similar order. There is no evidence at present to indicate that mental "work" is attended by any liberation of energy peculiar to it, or that mental excitement *per se* induces any noticeable metabolism. The results may be expressed in a general way by saying that "for every calorie which was transformed into external muscular work, four calories or more were transformed into heat, and left the body in that form. Whether the same ratio of efficiency applies to the muscular work of the internal organs has not yet been ascertained. Calculations of the total energy metabolized and the external work done during prolonged and severe muscular work by trained athletes (bicycle riders) indicate a far larger efficiency; but the results are attended with too great a degree of uncertainty to receive serious consideration without further corroboratory experimental evidence." There is little doubt that the utilization of energy in doing work is favorably affected by training.

Heat Production.—Finally, the subject of the metabolism of energy requires a brief mention of its relation to heat production. To what extent heat is produced for its own sake, *i. e.*, to maintain a definite temperature in the body, or whether it is to be looked upon solely as a waste product arising incidental to the metabolism occasioned by other physiological functions like muscular and glandular activity, is still a debated question. The temperature of man being approximately uniform, obviously changes in the thermal environment must affect the rate of dissipation of heat from the body or its production, or both. Changes in metabolism must thereby arise. Voit attempted to ascertain the extent of such changes many years ago by measuring the carbon dioxide production in a man of 70 kilograms body weight kept at different temperatures. The figures (per hour) found are given here:

TEMPERATURE.	CO ₂ IN GRAMS.
4.5 °C.	35.1
6.5 	34.3
9.0 	32.0
14.3 	25.8
16.2 	26.4
23.7 	27.4
24.2 	27.6
26.7 	26.6
30.0 	28.3

It will be observed that a "regulation" of metabolism in the sense of increased metabolism takes place only at the lower temperatures. At higher ranges, a "physical" regulation takes the place of the "chemical" or metabolic adaptation. At lower temperatures, it is by no means unlikely that the demand for heat is satisfied by direct combustion of body material—that is, a metabolism of energy,—whereas at ordinary tempera-

tures, the heat liberated in connection with the usual metabolic changes more than suffices to maintain the body temperature. The views on these points are somewhat divergent but the evidence seems favorable to the idea that, ordinarily, heat production is incidental to the metabolic processes and is sufficient to maintain the temperature of the individual above that of his surroundings. Whatever excess of heat may be produced is gotten rid of in various ways; for there is no evidence of diminished metabolism (and diminished generation of heat) with increase of external temperature. Heat is produced in excess. On the other hand, when external conditions are given in which this excess changes to a deficit, metabolic processes are provoked. At low temperatures, accordingly, a "chemical" regulation is inaugurated, not through direct intermediation of the food, but by increased protoplasmic activity.

On the basis of such views as have just been advanced, writers like Kasowitz maintain that substances such as alcohol, glycerine, lactic acid, etc., which are burned in the body without entering directly into the structure of the protoplasm, merely add to the heat already produced in excess, without doing any physiological work. They thus distinguish between the oxidative metabolism of integral tissue components and the combustion of unorganized compounds, holding that the latter are of use only under the relatively uncommon conditions where the heat production in the ordinary course of metabolism is insufficient. Such views have, however, been strongly combated.

The removal of the "waste heat" of metabolism is affected by a number of factors, such as the condition of the atmosphere, insolation, relative humidity, etc., which are subject to great variations. As Rubner has pointed out, the process of civilization has tended to eliminate, moderate, or equalize to some degree these external changes. There has thereby resulted a disposition on the part of the body of civilized man to lose some of the regulatory responses which primitively belong to him. It seems that increasing intelligence in respect to this department of hygiene will lead to noteworthy improvements in our modes of dress, and in the heating and ventilation of our habitations. The maintenance of heat equilibrium in relation to the mass of tissue involved and the size of the surface exposed—variations corresponding to large and small individuals—is apparently due to a nice adjustment of metabolism.

MODIFICATIONS OF METABOLISM.

Metabolism During Hunger.—The problems of metabolism are reduced to somewhat simpler terms when the behavior of the body during inanition is considered. The extreme case would be that in which all intake (of food and drink) is excluded, the respired oxygen being the only contribution brought to the organism from without. The features of hunger under less rigid conditions, *e. g.*, where water is taken, closely resemble the preceding ones in general character. For the physician and pathologist the subject possesses additional practical interest, in view of the fact that the essential derangements in many cases of under nourishment are qualitatively comparable with those noted

during complete starvation, the differences being of degree only. Von Noorden has well said that it is impossible to obtain a clear understanding of the metabolic changes which characterize or accompany disease, unless we can form some estimate of the implication of inanition in such changes. From this standpoint extreme hunger may, under certain relations, form the most extreme type of malnutrition.

In starvation, the body is living on its own tissues,—that is, katabolizing body constituents to liberate the energy requisite for the necessary bodily functions. As might be expected, the character of metabolism in inanition depends in no small degree upon the previous nutritive condition. It is necessary to bear in mind that a well-nourished organism with an abundant reserve supply of fat, glycogen, and proteid, may experience a response to the demands for energy somewhat different from that called forth amid less bountiful stores. Most of our information on this subject has been derived from experiments on animals; a few investigations on healthy men fasting over a considerable period of time will, however, be called upon to yield data for our consideration.

A question which early presents itself is this: How great are the losses which the body can sustain during hunger without serious impairment of function? The losses in body weight ascertained in the most carefully conducted researches on starving men are collected in the table below (Weber):

SUBJECT AND OBSERVER.	DURATION OF FAST.	BODY WEIGHT.		PERCENTAGE LOSS OF BODY WEIGHT.	
		At beginning.	At end.	Total.	Per day.
	Days.	Kilograms.	Kilograms.		
Cetti (Senator <i>et al.</i>).....	10	57.0	50.6	11.2	1.1
Breithaupt (Senator <i>et al.</i>)...	6	60.0	56.4	6.0	1.0
Succi (Luciani).....	30	63.2	51.8	19.0	0.6
Swede (Johannsen).....	5	67.8	62.8	7.4	1.5

These figures give no adequate idea of the losses undergone in more prolonged fasting, or of the resources of the body under such a trial. Kumagawa starved a bitch for ninety-eight days, during which time she suffered a loss of 65 per cent. in body weight (17 to 5.96 kilograms). The distribution of this loss varies somewhat with the amount of fat available. In the table on page 667 the changes in individual organs are calculated on 100 parts of the *fat-free* tissues. (E. Voit.)

These figures indicate the unequal disintegration of different organs. The adipose tissue suffers the earliest and greatest diminution. Among the residual (fat-free) organs, the glands will be noted to undergo a proportionately large loss, others—especially skin, central nervous system, and heart—experiencing less change. It has often been pointed out in this connection that the tissues suffering the relatively smaller losses include those whose function is of greatest importance for the continuance of life. Glycogen disappears from the body with varying readiness in starvation. The loss of proteid is extremely variable and in animals starved until death

the diminution of their proteid-content ranged, in E. Voit's experiments, between 22 and 49 per cent. These variations are attributable to the different fat reserves of the animals. Those which experienced the smaller losses (22 to 26 per cent.) showed a considerable supply of fat even after

ORGANS.	100 PARTS OF THE FAT-FREE ANIMAL CONTAIN—		100 PARTS FRESH FAT-FREE ORGANS LOSE—
	In good nutritive condition.	After starvation.	After 24 days' starvation.
Skeleton	14.87	21.50	5
Skin.....	10.30	11.29	28
Muscles.....	53.77	48.39	42
Brain and cord.....	0.94	1.11	22
Eyes.....	0.11	0.16	3
Heart.....	0.54	0.69	16
Blood.....	7.14	5.69	48
Spleen.....	0.39	0.26	57
Liver.....	3.98	3.05	50
Pancreas.....	0.33	0.19	62
Kidneys.....	0.66	0.45	55
Genitalia.....	0.20	0.23	49
Alimentary canal.....	5.81	6.02	32
Lungs.....	0.89	0.97	29

death. They suffered from proteid starvation; that is, certain essential organs must have experienced a loss of proteid greater than they could withstand. Presumably, these must have been specific *essential* organs, since most of the tissues can withstand a far greater loss—even 50 per cent.—than is here indicated. In those animals where a larger loss (49 per cent.) of proteid was noted, the fat had been reduced to a minimum; and the animals must have satisfied the demands for energy during the later days of starvation almost entirely with proteid. Here, then, we have both fat and proteid starvation. From a practical standpoint, it may be emphasized that all organs do not suffer the same degree of loss in under-nourishment; that some of them are able to protect themselves from extensive losses at the expense of other organs; and that the character of the losses is in no small degree variable with the previous nutritive condition.

Some of the characteristic features of metabolism in hunger are illustrated in the study of proteid metabolism—the aspect of starvation which has been most frequently investigated. The output of nitrogenous katabolic products tends to diminish after the earlier days of starvation, ultimately reaching a fairly constant level. This would seem to indicate that proteid katabolism is stimulated during the first two or three days; and the increased output of nitrogenous products during this period seems to vary somewhat in proportion to the richness of the previous diet in proteid. It is certainly unlikely that the high values for urinary nitrogen found in the earlier period of starvation are due to a liberation of retained excretory products which are suddenly swept out of the system under the altered nutritive conditions. In seeking to explain this repeatedly observed increase in proteid katabolism, Voit was led to make his well-known distinction between “circulating” and “morphotic” or “tissue” proteid in the body. The morphotic proteid is disintegrated only to a small extent in

the ordinary course of metabolism; that is, it represents the relatively stable nitrogenous component of the cells. The more readily metabolized circulating proteid, the supply of which is largely dependent on preceding conditions of nutrition, is used up during the early days of inanition. In this way the early high nitrogen output is explained by the Voit school. The succeeding fall in nitrogen excretion represents a stage in which other tissue components are destroyed in place of the residual and more stable morphotic proteid. Fat and glycogen now afford a part of the energy required. This explanation has, however, not received universal acceptance. In the few experiments made on man, this temporary increase in the rate of nitrogen katabolism has not always been as marked as in the experiments on animals. Among other explanations of the phenomenon a few deserve mention, especially because they illustrate what a wide range of complicating factors may influence the behavior of the body in metabolism. Thus, the "nutritive plane" of the individual has been called upon to account for the relatively high or low nitrogen output in the early periods of starvation. When the intake of nitrogenous food is suddenly cut off in young individuals accustomed to a high proteid metabolism, the cells do not at once adapt themselves to the new conditions, and the high rate of proteid katabolism is continued until new relations are gradually established. Again, a larger or smaller intake of water in starvation is effective, according to both Munk and Heilner, in increasing the output of nitrogenous compounds, although this is not usually the case when food is given. Finally, most of the prolonged starvation experiments on man have been undertaken with individuals in whom the reserve store of non-nitrogenous nutrients was relatively low. This, too, may help to account for the high output of nitrogen.

In brief periods of starvation some observers, notably Prausnitz, have regularly found a higher output of nitrogen on the second day than on the first. This is referred to the rapid consumption of glycogen during the early period of hunger, with a consequent protection of the proteid from decomposition. In animals a prolonged period in which the extent of nitrogen katabolism is fairly low and constant indicates a uniform progress of the decompositions in the body—a feature to which other facts likewise point. Finally, a period is reached in which the disintegration of body proteid rapidly increases, indicated by a twofold or threefold increase in the nitrogenous compounds eliminated. This "premortal" rise in nitrogenous output is the sign of impending death. By most investigators it has been referred to the exhaustion of the glycogen and fat depots of the body. When the latter are no longer available, the proteid resources become severely taxed and the tissues rapidly disintegrate to furnish the energy requisite for the bodily functions. Death is thus attributable to the lack of available nutrients in the tissues. The sudden premortal rise in nitrogen elimination has been ascribed by others to a sudden widespread disintegration of body cells due to the improper nutritive conditions to which they are finally subjected. The amount of materials available in the starving body before death intervenes may be very great—in animals as much as 70 per cent. of the original store of energy.

During starvation, heat production remains remarkably constant, and the body temperature is maintained until near the end, or the period where

	CETTI, 57 KILOS.		BREITHAUPF, 60 KILOS.		FLORA TOSCA.	
	Nitrogen output in urine, Grams.	Proteid equivalent, Grams.	Nitrogen output in urine, Grams.	Proteid equivalent, Grams.	Nitrogen output in urine, Grams.	Proteid equivalent Grams.
Before fasting.	13.49	84.9	13.02	82.0	13.99	87.5
1st hunger day.....	13.54	85.3	10.01	63.1	8.76	54.7
2d hunger day.....	12.58	79.3	9.92	62.5	8.38	52.3
3d hunger day.....	13.21	82.7	13.29	83.7	10.73	66.1
4th hunger day.....	12.39	78.1	12.78	80.5	9.40	58.7
5th hunger day.....	10.69	67.4	10.95	68.9	7.87	48.5
6th hunger day.....	10.10	63.6	9.98	62.2	7.73	48.5
7th hunger day.....	10.85	68.6	9.71	58.2
8th hunger day.....	8.90	56.1	7.70	48.0
9th hunger day.....	10.83	59.7	7.35	45.9
10th hunger day.....	6.90	42.4
11th hunger day.....	6.44	38.4
12th hunger day.....	6.07	43.5
13th hunger day.....	5.62	35.0
14th hunger day.....	4.08	25.4
1st eating day.	13.35	84.1	11.88	74.2	7.23	45.2

The actual extent of proteid katabolism during starvation is indicated by these data from experiments by Munk and by Van Hoogenhuyze and Verploegh.

profound metabolic changes give evidence of themselves in the sudden and rapid increase in nitrogen output. So far as has been experimentally observed the oxidative processes maintained during hunger do not decrease in extent below the values noted in the same individual under comparable conditions when food is not denied. This is apparently true not only in periods of rest, but likewise during work. The essential difference between the starving man and one in good nutritive condition (but temporarily without food) lies in the earlier onset of fatigue in the former. That is, "the muscles of the man are still capable of accomplishing practically as much in a single contraction during starvation as before; but they become exhausted more speedily. An important factor in this rapid fatigue is found in the extreme irritability and slight working capacity of the heart."

The metabolism of the elements other than nitrogen during prolonged starvation has not been extensively studied in man except in a few instances. The output of sulphur appears to run closely parallel to that of nitrogen, indicating a common source of the two elements in the disintegration of proteid. The elimination of phosphorus has been found to be increased both absolutely and relatively with respect to nitrogen. If the phosphorus excreted in starvation is likewise derived from proteids it should obviously bear the same relation to the nitrogen excreted as the two bear to each other in the body. This has not usually been the case. In addition to the high output of phosphorus, an increased elimination of calcium and magnesium, too great to be attributed to the disintegration of muscle tissue, has also been found. These facts, taken together, leave little doubt, that the bones, which are so rich in phosphates of the alkali earths, suffer loss.

Since the chlorides of the urine are primarily derived from the chlorides (chiefly NaCl) taken with the food, a rapid fall in the output of chlorides during starvation is naturally to be expected, and has repeatedly been observed. The writers have seen it sink to a small fraction of a gram in the early days of starvation in man, and continue at that level throughout a five-day hunger period. The excretion of potassium considerably exceeds that of sodium, quite the reverse of ordinary conditions. This observation adds another to the many evidences, during starvation, of the disintegration of the tissue elements (structures) in which potassium salts greatly preponderate.

So far as published experiments indicate, the formation of the fæces does not cease during prolonged starvation, although the quantities are greatly diminished. The composition of the "hunger fæces," *viz.*, the relatively high content of nitrogen (6 to 8 per cent.), fat, and inorganic salts, recalls the fæces discharged after an easily digestible diet, free from cellulose. This close resemblance has contributed largely to the prevailing view that the fæces are not to be considered as the undigested residue from food to any great extent under satisfactory conditions of diet, but rather as consisting in large part of secretory products from the alimentary tract.

We cannot attempt to follow the fate of the many other katabolic products arising during hunger, nor designate the specific changes produced in individual organs. One is impressed, however, by the slight extent of the variations from the normal which are met with. The differences between fasting and normal individuals are quantitative

rather than qualitative, at least during the earlier stages of starvation. Experiments of Abderhalden and others have demonstrated that the chemical make-up of the tissues which remain unused in a starving animal is not noticeably altered. The proportions of nitrogenous decomposition products obtainable are entirely comparable with those yielded by a well-fed animal of the same species. It is interesting to note that the fat content of the blood may be found notably higher during the early days of starvation. This corresponds with what might be expected if fat is transported during hunger from its storehouses in the body to the places where the oxidations take place.

With reference to the actual nutritive condition of the cells and their metabolic capacity in hunger, experiments by Schöndorff (1893) have given some evidence. He perfused the hind extremities of well-nourished and starving dogs with the blood of starving and normal animals, and estimated the metabolic power of the surviving body cells by the percentages of urea found in the blood. It was found that even when normal blood was perfused through the "hunger" limb, the proportion of katabolic products was smaller than that yielded by the well-nourished muscles. We may reasonably conclude from this that the metabolic activities of the cells are dependent upon their inherent nutritive conditions, as well as upon the character of the blood which supplies them. The extent to which individual organs may be impaired is seen in the case of milk secretion during hunger. Barbera (1900) saw the daily yield decrease under these conditions to one-seventh of its original volume in the course of fourteen days, all the constituents being involved in the change, although the yield of fat diminished most slowly. Lusk (1901) had a similar experience with a goat in which the output of milk could be diminished to far greater extent by a few days' starvation.

Closely related to the conditions pertaining in complete inanition or "acute" starvation, are those found in the more chronic forms of *deficient* nutrition ("Unterernährung") or malnutrition. Unfortunately we have few accurate experimental data on this subject—one highly important for the physician, within whose province it distinctly falls. The cases in which deficient nutrition may arise are numerous, and in all we have to deal with physiological conditions not markedly different from those discussed under complete hunger. It is possible that the organism adapts itself to the deficiency in intake by a more economical utilization of its resources, so that the body can maintain its nutritive equilibrium with a smaller expenditure of energy. Accurate data are not yet available in this direction, while evidence to the contrary is not wanting. Von Noorden believes that even after prolonged deficient nutrition an intake of 30 large calories per kilo of body-weight is required to maintain equilibrium. Practical experience, however, has shown that under poor nutritive conditions, persons may make gains on diets which are barely sufficient for the well-nourished individual. A careful study of this subject is important; for in conditions (such as gastric ulcer) where larger quantities of food cannot be consumed without danger, a knowledge of body needs, as demonstrated by actual experience, becomes invaluable.

In connection with the phenomena of metabolism peculiar to starvation, it is perhaps appropriate to mention the marked retention of

ingested materials which characterize what has been termed "re-alimentation"; that is, the return to normal conditions when food ingestion is resumed. In accordance with the general protection which the body affords in starvation to the organs most important for its survival, it has been noted that even prolonged starvation does not destroy the neuro-secretory apparatus. When food is again given, the digestive changes go on as usual. The glycogen content of the liver is rapidly reestablished and a decided gain is noted in the balance-sheet of intake and output of materials. This is especially true in the case of the inorganic salts as well as the nitrogenous intake. At present no extensive data applicable to man are available on this subject. An interesting illustration of the extent to which nitrogen may be retained is afforded by observations of Fr. Müller on a patient whose body-weight had fallen to 31 kilos during insufficient nutrition following stenosis of the œsophagus. After four days of absolute starvation with a daily loss of 4.28 grams of nitrogen, it became possible to increase the intake of food. During the following twenty-six days of feeding, the nitrogen balance was as given below:

	Daily intake of nitrogen.	Daily intake of food.	Daily output of nitrogen in urine and feces.	Nitrogen retention per day.
	<i>Grams.</i>	<i>Calories (large).</i>	<i>Grams.</i>	<i>Grams.</i>
5 days	7.60	765	5.91	1.69
7 days	8.99	881	7.04	1.95
8 days	11.77	1000	8.18	3.59
6 days	13.67	1100	8.83	4.84
26 days	42.03		29.96	

With every gain in proteid intake, a proportionately larger retention of nitrogen was noted. This is characteristic of convalescence from wasting disease, in which the katabolic processes preponderate. A similar retention of nitrogen is not readily brought about in the well-nourished organism in which nitrogenous equilibrium tends to be established very speedily.

Metabolism During Feeding.—Observations during conditions of starvation might, perhaps, be expected to furnish a satisfactory basis upon which to estimate the actual nutritive needs of the organism. In hunger, where one group of factors—the intake—can be entirely eliminated, it might appear that we are dealing with the simplest state of metabolic changes possible and that the data obtained would be broadly applicable. This, however, is only partly the case. For example, the relative quantities of proteid or fat decomposed per day in a starving individual are not necessarily indicative of the most advantageous utilization of materials, as the organism is compelled to employ the resources which are most easily available. It becomes important, therefore, to learn how the metabolic processes are modified when food substances are ingested.

Influence of Proteids on Metabolism.—The unique importance of proteids in nutrition, owing to their content of nitrogen, has already been mentioned. Since the body is unable to utilize other types of nitrogenous compounds in the entire absence of true proteids, except perhaps the immediate decomposition products of the latter, prolonged proteid hunger becomes as serious in its consequences as does the complete absence of food. Under suitable conditions a carnivorous animal like the dog can be kept in nutritive equilibrium on an exclusive meat diet. To accomplish this the animal must eat three to four times as much proteid as is decomposed during hunger. It has thus far been impossible to maintain similar equilibrium in man on an exclusive proteid diet. The failure to do so is associated, in part at least, with the inability to digest properly the enormous quantities of proteid requisite. It will be recalled that the net available energy of the proteids is smaller than their heat of combustion would indicate, owing to the incompletely oxidized products which are liberated from them. The digestive work which they entail is also not inconsiderable. The fundamental observations noted show that every increase in the amount of proteid fed tends to increase the katabolism of proteid. By virtue of the tendency of the body to adapt its nitrogenous katabolism to the proteid intake, it becomes possible to attain nitrogenous equilibrium with widely varying quantities of proteid. In all of these cases it is understood that the total intake of food must be sufficient to cover the demands of the body for energy. In the fasting condition the latter may amount, in the case of a man of average body weight, to somewhat over 2,000 calories per day, or 30 large calories per kilo of body weight. When food is taken, and no external work of any consequence is performed, the metabolism of energy is slightly increased over the fasting figure, perhaps to 32 to 33 large calories per kilo per day; while under conditions of muscular activity the demand for energy may be increased under extraordinary circumstances to 100 large calories per kilo per day or over.

Provided that these nutritive demands are satisfied, the absolute quantity of proteid required to prevent a loss of body proteid will depend somewhat on the proportion of non-proteid foods ingested and absorbed. A determination of the maximum quantity of proteid which can be utilized is scarcely feasible in the case of man, since it is practically impossible to exceed 200 grams in the intake without eliciting unpleasant symptoms. While it is true that most experiments in this direction have been carried out with meat as the chief source of the proteid, and that the extractive substances (such as lactic-acid salts, creatin, potassium salts, etc.) cannot be regarded as physiologically inert and non-toxic, yet there is no reason to believe that larger quantities of pure proteids of animal or vegetable origin could be consumed with relish for any length of time. Finally, certain considerations make it unlikely that a nutritive equilibrium could ever be established in man on an exclusive proteid diet.

While an increase of the proteids in the diet tends to augment proteid katabolism and leads to a greater elimination of nitrogen in proportion to the supply of proteids offered, an increase in the fat or carbohydrate constituents of the food tends to diminish proteid katabolism, although the latter cannot be completely stopped under any combination of diets.

An animal which receives a nitrogen-free diet of either fat or carbohydrate or both, will not succumb as soon as a starving animal. Nevertheless, the continued nitrogen losses during nitrogen (or proteid) hunger lead to a fatal result as inevitably as does complete inanition. More recent experimental work has, however, shown that in proteid starvation the loss of body proteid may become far smaller than the earlier investigators found. The essential feature in maintaining a lower plane of proteid metabolism in these cases consists in the administration of sufficient non-proteid nutrients to cover more nearly the demands of the organism for energy. This is well illustrated in experiments made by Folin on man. On a diet consisting of 400 grams of pure arrow-root starch and 300 cc. of cream containing 15 to 25 per cent. of fat, together with a few grams of salt, the daily output of nitrogen was reduced to between three and four grams in all the individuals under observation over a period of several days. This effect appears to be common to both fats and carbohydrates, although in different degree.

Effects of Non-Nitrogenous Nutrients on Proteid Metabolism.—The effect of carbohydrate and fat on the metabolism of proteids under conditions in which the total nutritive demands are more nearly satisfied is deserving of closer attention. Although these non-nitrogenous nutrients cannot check the katabolism of body proteid in proteid hunger, they are capable of exerting a definite and important influence in diminishing the extent of proteid katabolism. This is usually spoken of as the *proteid-sparing* action of fats and carbohydrates. Most of the data in demonstration of this have been collected from experiments on animals. The following experiment by von Noorden and Dieters illustrates the proteid-sparing action of carbohydrates in man. The daily nitrogen intake during a period of four days amounted to 12.6 grams, with a daily output, in the urine, of 10.4 grams of nitrogen. When, on the fifth day, 200 grams of cane-sugar were added to the diet the urinary nitrogen fell to 9 grams. According to this, 1.4 grams of nitrogen (equivalent to 13 per cent. of the previous output) had been spared in the form of proteid. Similar proteid-sparing effects have been obtained with fat. The experience of all observers agrees in indicating the superiority of carbohydrates over fats in this respect. Voit found an average decrease in proteid metabolism of about 7 per cent. with fats and about 9 per cent. with carbohydrates. A comparison which Kayser instituted upon himself is interesting: with an intake of (in round numbers) 132 grams of proteid, 70 grams of fat and 340 grams of carbohydrate, having a fuel value of 2,600 large calories, he was able to maintain nitrogenous equilibrium. The replacement of carbohydrate in the food by an "isodynamic" amount of fat (140 grams) caused an increase in the output of urinary nitrogen and a consequent negative balance, in contrast with the preceding slight gain. It should be noted, however, that possible differences in the relative availability of the supposedly "isodynamic" quantities of fat and carbohydrate have not been drawn into consideration by most investigators.

The methods of estimating the protective power which the different foodstuffs exert upon tissue constituents, other than proteids, are indirect and too complicated to be referred to here. Marked differences in the role of the fats and carbohydrates of the food in sparing body-fat have not been made out. The preceding discussion of the relations of metab-

olism to the food supply has indicated the "flexibility in the animal organism as regards the nature of the material consumed in its vital processes." Armsby has well summarized the range of choice by the organism and the mutual replacement of nutrients. "The amount of proteid material necessarily required for the metabolism of the mature animal, we have seen to be relatively small. Aside from this minimum, the metabolic activities of the body may be supported, now at the expense of the body-fat, now by the body proteids, and again by the proteid, the fats, or the carbohydrates of the food. Whatever may be true economically, physiologically the welfare of the mature animal is not conditioned upon any fixed relation between the classes of nutrients in its food supply, apart from the minimum requirement for proteids. The possibility of a mutual replacement of the several classes of nutrients in the food follows almost necessarily from the power of the organism to utilize them all indifferently (in a qualitative sense at least)."

It is appropriate to consider the influence exerted upon metabolism by a number of substances which cannot properly be classed among the typical, foodstuffs, but nevertheless may enter to an important extent into the make-up of the diet. Among the nitrogenous compounds, gelatin stands foremost. Although closely related to the true proteids, gelatin is sufficiently characteristic and peculiar in its chemical make-up to be classed in the group of albuminoids (proteoids, scleroproteins). Chemically it differs from proteids in the absence of the tyrosin- and tryptophan-yielding groups, the small content of sulphur-containing radicals, and the peculiar quantitative distribution of its constituent organic complexes. Experiments both on man and on animals have demonstrated the failure of gelatin to prevent loss of body proteid when it is the sole nitrogenous compound fed. It can, however, replace proteid to a very large extent, and it acts conspicuously in sparing both proteid and fat in the body. In the absence of other forms of nitrogenous substances, animals fed on gelatin with non-nitrogenous nutrients succumb within a few weeks. Careful experiments by Murlin, in Lusk's laboratory, have suggested the following conclusions: A mixed diet, more than covering the energy requirement of the organism, and containing two-thirds of the starvation minimum of nitrogen in the form of gelatin, and one-third in the form of proteid, will maintain nitrogenous equilibrium for a few days at least. In other words, the proteid requirement under the combined sparing action of gelatin, fat, and carbohydrate falls to one-third the starvation requirement. Experimental data obtained on animals by C. Voit and by I. Munk show that 100 grams of gelatin will protect about the same quantity of proteid as is spared by 200 grams of carbohydrate. Body-fat, likewise, can be protected by gelatin feeding. As might be expected, the gelatigenous tissues (tendons and cartilage) exert a similar proteid- and fat-sparing action to the extent to which they are digested and converted into gelatin in the alimentary tract.

The influence of other nitrogenous compounds, such as proteoses, peptones, amino-acids, and amides, upon proteid metabolism, has not been studied in man. Undoubtedly these substances, especially the immediate derivatives of the proteids, can replace the latter to a certain extent; but under ordinary circumstances they are unimportant. Among the non-nitrogenous ingesta, cellulose, owing to its indigestibility, plays

little if any part, further than to increase the nitrogenous waste leaving the body when large portions of indigestible foods are fed. The few data available on the action of pentoses—the five-carbon sugars like arabinose, xylose, and rhamnose—upon proteid metabolism disclose no marked effects. The fatty acids have been found to exert a proteid-sparing influence quite comparable with that of the fats from which they are derived; while the remaining component of the latter, the glycerin, appears to be negligible in this regard when equivalent doses are used.

Alcohol.—Among the substances which may influence proteid metabolism, alcohol deserves mention because of its widespread use. The views regarding its value as a food and its influence on metabolism are somewhat divergent, and some of the testimony has not always been free from bias. That it is in large measure burned in the body seems reasonably certain, at least as far as this applies to moderate quantities. We must, however, distinguish carefully between large doses which have an unmistakable toxic action, and smaller doses in which the alcohol appears to exert a protective action on proteid and fat. Neubauer has observed that in severe diabetes administration of alcohol may check the output of acetone much as carbohydrates do. In careful metabolism experiments by Atwater and Benedict, results with ordinary diet were compared with those in which part of the fats and carbohydrates of the food were replaced by the isodynamic amount, about 72 grams ($2\frac{1}{2}$ ounces), of absolute alcohol. This is about as much as would be supplied in a bottle of claret, or 6 ounces of whisky, or 5 ounces of brandy. The quantities of alcohol eliminated by the lungs, skin, and kidneys, varied from 0.7 to 2.7 grams, and averaged 1.3 grams per day. Over 98 per cent. of the ingested alcohol was oxidized in the body, and one gram of alcohol was calculated to be isodynamic with 1.73 grams carbohydrate or 0.78 gram of fats of ordinary food materials. The proportions of food and of the several kinds of nutrients made available for use in the body were practically the same in the experiments with and those without alcohol in the diet. The potential energy of the alcohol was transformed into kinetic energy in the body as completely as that of ordinary nutrients. The efficiency of alcohol in the protection of body fat from consumption was very evident. The losses of fat were no larger and the gains no smaller with alcohol in the diet than with the corresponding diet without alcohol. In this respect there was no indication of any considerable difference between the alcohol and the nearly isodynamic amounts of fats and carbohydrates which it replaced. The efficiency of alcohol in protecting body protein was evident, but not fully equal in this respect to the isodynamic amounts of the ordinary nutrients, the result depending somewhat on the extent to which the individual was accustomed to the use of alcohol. We may repeat with Atwater and Benedict, "that there is a very essential difference between the transformation of the potential energy of the alcohol into the kinetic energy of heat, or of either internal or external muscular work, and the usefulness or harmfulness of alcohol as a part of ordinary diet."

It would be a mistake, however, to assume that alcohol can be rated as a true non-nitrogenous food in the sense in which fats and carbohydrates are foods. For experiments have shown that alcohol prior to

its combustion in the body exerts a noticeable influence upon the metabolic processes in the liver, and possibly in other organs, whereby a marked effect is produced upon the output of uric acid. In other words, alcohol, and especially alcoholic drinks, when taken with purin-containing foodstuffs, exert a direct influence upon the metabolism of those compounds which give rise to exogenous uric acid, increasing largely the amount of uric acid excreted (Beebe). Whisky, for example, may be given with impunity when the patient—as in typhoid fever—is on a light or purin-free diet, without materially influencing the production or output of uric acid; but when the alcoholic fluid is taken with a hearty meat diet, or with any diet containing free or combined purin compounds, the system is at once liable to show the effects of the excess of uric acid. In this respect alcohol behaves quite differently from an ordinary non-nitrogenous food.

The literature abounds in studies regarding the influence of a large variety of substances, both organic and inorganic, upon metabolism. Some of these, like the drugs, cannot be considered here; others, like tea, coffee, and various dietary accessories, exert no profound action on the organism in moderate dietetic quantities. In recent years food preservatives, such as borax and boric acid, sulphites, benzoic and salicylic acids, formaldehyde and fluorides, have received special consideration in view of their increasing and widespread use. At the present time it would be unprofitable to generalize from these studies.

Role of Inorganic Salts.—The inorganic constituents of the diet possess a significance in no degree commensurate with their lack of energy-yielding qualities. The elements which they include are essentially sodium, potassium, calcium, magnesium, iron, phosphorus, sulphur, chlorine, and silicon—which are distributed in widely varying proportions in different parts of the body, about 83 per cent. belonging to the skeleton and the remaining 17 per cent. to the soft parts. The quantitative relationship is shown in the following table summarized from Söldner's analyses of the bodies of infants:

GRAMS PER KILOGRAM OF BODY WEIGHT.

K ₂ O.....	1.87	Al ₂ O ₃	0.03	SO ₃	0.54
Na ₂ O.....	2.04	Fe ₂ O ₃	0.22	Cl.....	1.76
CaO.....	10.12	Mn ₃ O ₄	0.007	SiO ₂	0.02
MgO.....	0.38	P ₂ O ₅	10.01	CO ₂	0.14

That a growing organism must be supplied with the inorganic constituents necessary for the proper development and organization of the tissues is self-evident. It is interesting to note that in milk, nature has supplied the infant with an admirable diet in respect to the needs for inorganic constituents. Milk is richer in calcium, so essential to the development of the skeleton, than any other common dietary article except the egg, which in turn is the storehouse of materials furnished to those young which have an extra-uterine development. The splendid adaptation to the relative needs of growing young, which Bunge has called attention to in the case of the milk of different species, is well worthy of careful study. His investigations have shown that the rapidity of growth of man and the domestic animals during lactation is propor-

tional to the composition of the milk. As regards calcium and phosphorus, two elements especially concerned, this feature is striking.

Time in which the body-weight of the new-born animal was doubled (in days).	One hundred parts of milk contain			
	Proteid.	Ash.	Calcium.	Phosphoric acid.
Man..... 180	1.6	0.2	0.328	0.473
Horse..... 60	2.0	0.4	1.24	1.31
Cow..... 47	3.5	0.7	1.60	1.97
Goat..... 19	4.3	0.8	2.10	3.22
Pig..... 18	5.9
Sheep..... 10	6.5	0.9	2.72	4.12
Dog..... 8	7.1	1.3	4.53	4.93
Cat..... 7	9.5

The effects of a lack of certain of the inorganic salts in the diet have long been familiar in the case of the adult, as well as the growing young. A deficiency of calcium giving rise to rachitic conditions in the child has its analogue in the osteoporosis of the adult. We have taken occasion to refer to these facts, because they illustrate the important role of inorganic compounds in the metabolism of growth and direct attention to similar functions of these compounds in adult life. In health, the adult is continually losing inorganic salts, not only so long as they are contributed to the body with the diet, but equally well when there is a deficiency of them in the intake. Experimental observation shows that with adequate nutrition there is, in the full-grown individual, a tendency toward "salt equilibrium." The latter condition is apparently subject to far more extensive fluctuations than is the case with the organic foodstuffs; but it is as yet impossible to frame any general laws bearing on the indirect influences of the inorganic food constituents on the metabolism of the energy-yielding compounds. There is here a broad field for fruitful research. Sufficient facts are at hand to indicate the promising character of such studies. For example, lack of sodium chloride in the food soon leads to deficient secretion of hydrochloric acid in the gastric juice. Animals fed for long periods of time on foods deficient in calcium, but rich in organic nutrients, are extremely susceptible to intoxication with organic acids, like lactic or oxalic acid. Since the latter may be formed at times in the intermediary metabolism of carbohydrates, in certain perversions of metabolism their toxic action may be traced directly to the lack of neutralizing or "antitodal" (disintoxicating) inorganic bases in the diet.

The profound osmotic effects which the inorganic salts of the body fluids are concerned in; the phenomena of saline diuresis and acceleration of lymph-flow; the unique types of salt glycosuria; the marked effects on the muscular and nervous structures; and the peculiar antagonistic relations of differentiations such as sodium, potassium, and calcium, leave no doubt of the importance of the inorganic foods in modifying metabolic processes. At present we can scarcely go beyond the realm of interesting speculations. We need further to be instructed not only regarding the quantitative needs of the animal body in the case of the individual elements, but also regarding the forms (or types of compounds)

in which these are best rendered available. Many of the elements exist in nature in organic combinations, conspicuous in the case of certain foods.

The determination of the nutritive requirements of the body for these inorganic compounds properly belongs to the subject of dietetics. One of the difficulties in arriving at a correct understanding of the metabolism of the inorganic salts has arisen from a lack of knowledge regarding the channels by which they leave the body. Iron furnishes a good illustration of some of the errors formerly encountered. The failure to recognize the intestinal epithelium as a factor concerned in the removal of iron naturally allowed a false interpretation to be placed on the occurrence of this element in the *fæces*. To the earlier observers, iron in the stools was a direct indication of lack of iron-absorption, particularly in view of the extremely scanty elimination of ferric salts usually noted in the urine during the same period. But the establishment of the fact that the gut may be directly concerned in the excretion as well as in the absorption of iron compounds, made possible a new interpretation of the earlier observations. Iron might be present in the alimentary canal, either owing to failure to be absorbed, or equally well because it had been discharged into this channel, through the epithelial walls. It became necessary to follow the paths of elimination when the introduction of this element directly into the alimentary canal was avoided. Since it has been found that iron may be introduced subcutaneously or even directly into the blood current, without producing any marked increase in the output through the urine, while the *fæces* may contain noticeable quantities, the significance of the intestine with reference to the elimination of such elements becomes apparent.

The part which the inorganic salts may play is thus manifold and difficult of interpretation. No energy is set free in their oxidation; yet they may exert most subtle influences, if such examples as the assumed profound physiological function of the iodine present to the extent of a few milligrams in the thyroid glands are to be trusted. So far as can be judged at present, Liebig was quite correct in pointing out that the inorganic salts are not an accidental contamination of living matter, but rather of fundamental importance.

Work and Metabolism.—Among the influences which affect metabolism, muscle-work is perhaps of even greater significance than the food intake. The effects are immediate and the extent of the change produced is far greater than the mere measure of the work done would seemingly indicate; for the most part, the skeletal (voluntary) muscles outrank the non-striated (involuntary) ones in the extent to which they participate in these effects. When a muscle contracts, heat is liberated, and work is done. The relative distribution of the energy between these two effects varies somewhat with the conditions under which the contraction is carried out. Within certain limits, as Fick demonstrated, the working capacity increases with the demand made upon the muscle. For example, a muscle which under slight stimulation transformed 6 per cent. of the energy used into work done, performed work up to 29 per cent. of the total used when its most vigorous efforts were called out.

The law of the conservation of energy, which we have seen to hold for the body, teaches that the various manifestations of energy, such as heat, work, etc., can be expressed in common terms; and the relation between heat and mechanical work is shown in the equation, 1 large calorie = 425 kilogrammeters. On this basis, the potential energy of the foodstuffs can be expressed in terms of the maximum work which they can afford, approximately as follows:

1 gram of proteid yields.....	1,700 kilogrammeters.
1 gram of fat yields.....	4,000 kilogrammeters.
1 gram of carbohydrate yields.....	1,700 kilogrammeters.

Actually, however, much larger quantities of the foodstuffs must be katabolized to yield mechanical work in this amount; roughly, about one-fifth to one-quarter of the total energy is thus convertible. The extent to which metabolism may be increased by work under normal conditions is best illustrated by actual figures. In experiments covering forty-nine days on healthy adults, the average total energy given off per day during rest, with food, was 2,262 large calories; during work in the same individuals, over sixty-six days, the daily average was 4,676 large calories. Of this twofold increase (2,400 calories), 450 calories were equivalent to the extra muscular work done. Rubner has calculated the total metabolism of a large number of individuals, on the basis of an average body weight of 70 kilos, and expressed the results in heat units (kilocalories), thus:

During rest.....	2,303 calories = 32.9 calories per kilo.
Slight bodily work (physicians, etc.)	} 2,442 calories = 34.9 calories per kilo = 6% increase.
Medium bodily work (soldiers, etc.)	
Severe work (machinists, etc.)	} 2,868 calories = 41.0 calories per kilo = 24% increase.
Exhausting work (miners, etc.)	
	} 3,362 calories = 48.0 calories per kilo = 45% increase.
	} 4,790 calories = 68.4 calories per kilo = 108% increase.

The influence of muscular work on metabolism is speedily made evident by an increased consumption of oxygen and output of carbon dioxide. The relation between the oxygen inspired and the carbon dioxide expired, *i. e.*, $\frac{\text{CO}_2}{\text{O}}$ is known as the respiratory quotient; normally this is less than 1. Not all of the oxygen reappears again in the eliminated carbon dioxide, since some of it is used in the oxidation of other elements to form water, sulphuric acid, and other bodies. In the combustion of pure carbon, one volume of oxygen yields one volume of carbon dioxide. The ratio $\frac{\text{CO}_2}{\text{O}}$ in this case is unity. In the body, however, the magnitude of the respiratory quotient depends on the nature of the katabolized substances. For the combustion of carbohydrates it is approximately 1; in the katabolism of proteids it is about $\frac{1}{10}$; and for fats the ratio falls to $\frac{1}{70}$. The respiratory quotient will accordingly vary in accordance with the relations here expressed, and may afford important information regarding the nature of the katabolic processes. Experience has shown that the consumption of oxygen by the tissues is independent, within wide

limits, of the oxygen supply, but varies directly with the demands of the tissues. In view of this, the extent of oxygen consumption may be taken as a measure of the action of different influences on the rate of metabolism. Studies have been made on the effects of walking, marching, swimming, mountain climbing, etc., upon respiratory metabolism. Zuntz and Katzenstein have estimated the intensity of the metabolic changes which work brings about in man. Expressed in the consumption of oxygen per minute, in contrast with the conditions prevailing during rest, they found: During rest 263 cc., walking on level 763 cc., walking up hill 1,253 cc. These are quite comparable with the observations made by Zuntz and Schumburg on soldiers at rest, and marching with and without accoutrements. The total change in the daily excretion of carbon dioxide resulting from work is shown in experiments on a man of twenty-three years of age. During the periods of ordinary work, the heat equivalent of the external muscular work amounted to about 11 per cent. of the total energy metabolized.

DAILY ELIMINATION OF CARBON DIOXIDE IN THE SAME INDIVIDUAL.

(From experiments by Atwater and Benedict.)

Rest, without food.....	676 grams
Rest, with food.....	812 grams
Work, with carbohydrate in diet....	1,820 grams
Work, with fat in diet.....	1,665 grams
Extra severe work, with fat in diet...	3,073 grams

Higley and Bowen have made a study of the immediate changes in the excretion of carbon dioxide incidental to muscular work in bicycling. The results agree with those of previous workers in indicating a uniform output of carbon dioxide during uniform work. The changes which give rise to this katabolic product in the muscle may be pictured as beginning instantly with the commencement of the work. Since the gas must first diffuse into the blood and then be carried to the lungs, there should be a latent period of a little more than half the time required for a complete circuit of the blood before the first waste product formed during work can be exhaled. A variation of several seconds may reasonably be expected, dependent upon the rapidity of the circulation. The latent period of increase in the output of carbon dioxide from the lungs in case of beginning work is nearly twenty seconds, the increase reaching its maximum in about two minutes. Upon cessation of work, the output decreases again to the normal amount in about the time occupied by its increase and after a like latent period.

In view of the rapid adjustment of the carbon dioxide output to the muscular metabolism occurring, it might be expected that the extra elimination during work would be confined almost entirely to the day time when the work is done. This is actually the case; and during the night periods it is only a little larger in the work experiments than in the rest experiments.

The proportions of carbon dioxide, water, and heat, eliminated during the different periods of the day in the same individual at rest and at work, with and without food, are shown on page 681 (Atwater and Benedict).

It is well known that a given amount of mechanical work is not always done at the same cost of materials metabolized. Training and fatigue

		CARBON DIOXIDE.						WATER.						HEAT.							
		Rest. Fasting.		Rest. Food.		Work. C'by diet.		Rest. Fasting.		Rest. Food.		Work. C'by diet.		Rest. Fasting.		Rest. Food.		Work. C'by diet.		Work. Fat diet.	
Day Period		Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
}	7 A. M.—1 P. M.....	28.04	28.37	38.11	38.57	76.70		27.46	26.36	39.46	40.12	28.35	29.07	37.90		38.13					
	1 P. M.—7 P. M.....	25.53	28.57	38.75	38.13		23.13	26.08	41.87	40.78		25.74	28.08	38.33		37.46					
	Total, 12 hours.....	53.57	56.94	76.86			50.59	52.44		81.33	80.90		54.09	57.15	76.13		75.59				
}	7 P. M.—1 A. M.....	24.73	24.21	14.29	13.83		24.46	24.58	10.74	10.84		24.69	24.12	14.41		14.46					
	1 A. M.—7 A. M.....	21.70	18.85	8.85	9.47		24.95	22.98	7.93	8.26		21.22	18.73	9.46		9.95					
	Total, 12 hours.....	46.43	43.06	23.14	23.30		49.41	47.56		18.67	19.10		45.91	42.85	23.87		24.41				
Total, 24 hours.....		100.00	100.00	100.00	100.00		100.00	100.00	100.00	100.00		100.00	100.00	100.00		100.00					

are important factors in considering the expenditure which a given muscular task calls for. In general, the trained and untired muscle is the more economical; that is, it transforms less material in doing a given amount of work than does the untrained or fatigued muscle. Other circumstances, among which are atmospheric conditions (oppressive heat, humidity, etc.), the relative strain on specific muscular parts, the absolute amount of work to be done, as well as personal factors—all influence the capacity for work and the relative expenditure of energy. The importance of an adequate knowledge of the factors which influence the capacity for work has been emphasized by the study of Zuntz and Schumburg on soldiers during marching. Apparently minor considerations, such as comfortable or uncomfortable adjustment of the knapsack, irritation of the skin, improper clothing, and overweighting, may be sufficient to occasion an increased expenditure of energy entirely disproportionate to the work done. Again, in bicycling, the influence of the speed on the energy utilized per kilo of body weight and 1,000 meters distance covered were found by Leo Zuntz to vary as follows:

At a speed of 60 meters per min., 40.3 cal. = 552 cal. per kilo. per 1,000 meters.
At a speed of 100 meters per min., 47.2 cal. = 647 cal. per kilo. per 1,000 meters.
At a speed of 143 meters per min., 78.5 cal. = 1,075 cal. per kilo. per 1,000 meters.

The increased expenditure of energy which is called forth by those exertions which ordinarily pass unnoticed may be not inconsiderable. The mere maintaining of the body in an upright position calls for a consumption of 10 to 20 per cent. more oxygen than is used in quiet repose. The varied activity of the hands and arms makes corresponding demands on the energy supply. Wolpert has estimated the increase of CO_2 output in people engaged in various occupations over the quantities observed for the same individuals at rest, as follows:

In a seamstress the increase was 13 per cent.
In a bookkeeper the increase was 17 per cent.
In a tailor the increase was 22 per cent.
In a shoemaker the increase was 47 per cent.

These differences are obviously attributable to the different degree to which the hands and arms are employed, the general (sitting) posture being maintained in each case. In sleep we have the extreme contrast to muscular activity in work; and although the consumption of oxygen and the output of carbon dioxide, for example, fall to about three-fourths of the figure quoted in the waking state, it is scarcely less than what can be attained by complete relaxation during waking hours. Johansson observed an hourly CO_2 elimination of 22 grams during sleep; of 31 grams during waking rest. In general, we may say that there is an increase of about 40 to 45 per cent. in carbon dioxide output during waking rest over absolute relaxation; a figure which illustrates the physiological significance of repose in therapeutics. With a patient reduced to a minimum of strength and store of surplus energy, rest (in the sense of complete relaxation) can well be advised as an important protective measure, on the basis of sound physiological evidence.

In addition to external muscular work, we may also call attention to another form of activity partly muscular, which is associated with diges-

tion. The following figures, calculated from experiments made in Zuntz's laboratory, indicate the relation of the digestive work accomplished to the heightened metabolism, in terms of the percentage increase in carbon dioxide excreted and oxygen consumed (in daily averages):

Heat value of the food absorbed.	Increase in carbon dioxide produced.	Increase in oxygen consumed.
<i>Calories.</i>	<i>Per cent.</i>	<i>Per cent.</i>
2,233	16.3	12.2

The same facts may be expressed from another standpoint, by noting that in rest the amount of energy expended when fasting is only about 10 per cent. less than with food.

We have reserved any discussion of the influence of muscular work upon nitrogenous metabolism for this place, because it bears directly upon the question of the source of the energy transformed in this condition of bodily activity. Is work done at the expense of proteids, fats, carbohydrates, or two or more of these body constituents? With respect to the proteids, the problem admits of a ready experimental answer. If an individual is maintained in nitrogenous equilibrium upon an *adequate mixed diet*, the effect of muscular activity ought to manifest itself in a distortion of the nitrogen balance if proteids are katabolized to supply energy for work. It seems obvious that if an individual is fed over long periods on a ration largely or exclusively composed of proteids, the source of muscular work must be found in increased proteid katabolism. Similarly when the supply of non-nitrogenous food is inadequate to furnish all the energy needed, the conclusion is inevitable that nitrogenous compounds will be disintegrated to supply the demands. In accordance with this, it has been observed that animals fed over long periods of time on lean meat alone are capable of performing severe muscular labor. Although the nitrogenous excretion has been observed to be increased under such conditions, the proteid katabolized was too small to account for the energy expended in the work; such experiments, however, give no sufficient reason for concluding that the body performs work *preferably* at the expense of proteid material. What do observations made under other conditions of diet teach?

It may be profitable to review the history of physiological views on the sources of muscular energy. Liebig early assumed that proteids are decomposed in the body to yield the energy of mechanical work—a view which is, in a certain sense, still shared by Pflüger. Observations by Pettenkofer and Voit soon made such a position appear untenable; for they failed to find the increase in urea excretion which might have been expected during increased muscular exertion. Further, the experiments made it clear that the non-nitrogenous nutrients must be the sources of the energy available under these conditions. The classic experiment of Fick and Wislicenus (1866) was, perhaps, the first satisfactory attempt to compare the energy expended during work with that rendered available by the proteid disintegrated. They calculated that the quantity of proteids katabolized during an ascent of the Swiss Faulhorn (6,500 feet), and measured by the urea excreted, was insufficient

to account for more than a small fraction of the energy required to raise their bodies to the height of the mountain, not to mention the energy expended in the work of the internal organs and muscular movements not directly involved in the ascent.

Contrary to these results, various investigators have found more or less increase in proteid metabolism after muscular work. In those instances, it has usually been found that the diet selected was insufficient for the demands made upon the body. Where the food supply has been in excess of the amount required for maintenance, any material increase in the nitrogen excretion as the result of the work done has usually been overlooked. As an illustration of conditions where daily losses of nitrogen amounting to 5 to 8 grams were noted during severe muscular work, we may quote the observations of Atwater and Sherman on bicycle riders in six-day races. Analyses of food, urine and faeces are summarized below, in terms of daily averages:

RIDER.	NITROGEN.				EQUIVALENT LOSS OF BODY PROTEIN.
	In food.	In faeces.	In urine.	Loss.	
	Grams.	Grams.	Grams.	Grams.	Grams.
Miller.....	29.4	1.8	36.2	8.6	53.8
Albert.....	29.1	2.5	33.7	7.1	44.4
Pilkington....	36.0	2.2	38.9	5.1	31.9

The exertion in these races was very severe, the riders averaging eighteen and a half to twenty hours of work and a distance of over 300 miles a day. There was, unquestionably, a deficiency of non-nitrogenous nutrients in the diet which was evidently poorly selected and inadequate, and it is quite conceivable that equally severe and prolonged exertion might be undergone without increased metabolism of nitrogen, provided the supply of non-nitrogenous fuel material was abundant.

In the studies of Zuntz and Schumburg on soldiers during marching, an increased elimination of nitrogen was observed on the marching days and the rest days immediately succeeding them. It was noted that the increased katabolism of proteid would account for not more than 6 to 7 per cent. of the extra work accomplished; furthermore, the increase in nitrogenous waste was in no way proportional to the absolute amount of work done, but was essentially influenced by the severe heat and other oppressive atmospheric conditions. Further, there was no change in the distribution of the nitrogen in the various types of urinary constituents during work. One feature during work deserves mention, namely, the noticeable increase in nitrogen eliminated in the perspiration. Under conditions of profuse sweating during active exertion, the daily output through this channel may, according to Benedict, become as high as 0.22 gram per hour—a quantity by no means negligible in accurate balance experiments.

The increase in the excretion of nitrogenous waste during extreme activity may reasonably be attributed to a decomposition of tissue protoplasm, incited perhaps by fatigue or deficient respiration in individual

groups of muscles, as Speck has maintained. In many experiments made in this country, under the auspices of the Department of Agriculture, no similar influence has been found; and no evidence whatever has been obtained to indicate that proteids are the sole source of energy in muscular work. Armsby has well summarized the evidence now available:

"1. The non-nitrogenous ingredients of the food or of the tissues are the chief source of muscular energy. In by far the greater number, if not all, of the experiments upon this subject the amount of proteid metabolized, as measured by the nitrogen excretion, was insufficient to furnish energy equivalent to the work done, the deficiency being in many cases very great. This statement, it will be observed, does not assert that the proteids are not concerned in the production of this energy. We may regard it as very probable that the non-nitrogenous matter metabolized has first entered into the structure of the muscular protoplasm, which, as we know, consists largely of proteids; but in a contraction it is largely, if not wholly, the non-nitrogenous groups contained in the protoplasm which are metabolized rather than the nitrogenous groups.

"2. With insufficient food there may be a considerable increase in the proteid metabolism, as a result of muscular exertion, especially when pushed to exhaustion.

"3. This increase is far from sufficient to supply energy for the work actually done, is not proportional to it, and seems dependent to a considerable degree upon accompanying conditions.

"4. With sufficient food the increase of the total proteid metabolism consequent upon muscular exertion is at the most slight and possibly equal to zero.

"5. In some cases a storage of proteids has been observed to result from the performance of work."

It would be a mistake to conclude that the proteids of the body play no part in the work of its muscles. The muscle protoplasm is built up of both nitrogenous and non-nitrogenous components; and while the readjustments which take place during the contractile processes involve a destruction of the non-nitrogenous constituents, perhaps in the form of sugar or glycogen, both components appear to be requisite for the proper maintenance of an active working apparatus. It is thus quite conceivable that with an inappropriate proteid supply muscular power might be impaired seriously, even though the liberation of energy in the actual contractile changes goes on at the expense of the carbohydrate groups of the protoplasm. We may picture the latter as a labile substance when the easily detached non-nitrogenous groups are joined to it. Muscular activity would accordingly involve a change in the stability of the protoplasm, which in turn would resume its original condition of irritability by becoming regenerated through the addition of fresh carbohydrate groups. Several experimental observations are more easily interpreted from this point of view. For example, it becomes evident that proteid alone will not accomplish the regeneration of the contractile substance in a satisfactory degree, although in its disintegration it may furnish a considerable proportion of non-nitrogenous groups—the so-called "carbon moiety" of the proteid molecule. Again, if the proteids form a semi-passive agent, as it were, in the development of muscular power, it is plain why the muscles may be more capable of retaining pro-

teid when they are active, than is the case with inactive or less vigorously working muscles. Herein lies the explanation of the phenomena of muscular hypertrophy; and experiments have indicated a greater tendency for the body to gain proteid during light work and abundant diet, than is observed in a less active condition. We have here indicated the distinction between "putting on flesh" (growth of muscle), and storing up foodstuffs. The bearing of this reciprocal relation between exercise and muscular growth and its connection with the metabolism of muscle, is not without physiological importance. We must distinguish between the *development* of a well-organized muscular system calling for a liberal proteid supply, and the maintenance and *working* demands of such organs—*i. e.*, between the construction of the machine and its energy requirement. Finally, the participation of the body proteids may apparently be provoked by unfavorable conditions for muscular work, to some of which reference has already been made and among which oxygen starvation is a conspicuous example. Thus, in the muscular exertion of dyspnœa the increased proteid decomposition seems to be attributable to local conditions in the muscles involved. The katabolic processes in these organs are qualitatively altered and fatigue products are more speedily formed. That proteids are not the only components affected in this perverted function, is seen by the disturbances evoked in the carbohydrate constituents of the muscles, whereby such compounds as lactic acid may arise in considerable quantities.

At present, it is practically impossible to ascertain with certainty what choice, if any, the body exercises between fats and carbohydrates in the decomposition of non-nitrogenous compounds in muscular work; nor can we say that the fats are transformed into sugar or glycogen before they become available for the immediate work of the contractile tissues. The more recent studies upon isolated muscles, especially the heart, are very suggestive. These show that such organs can maintain active contractions for many hours, when they are supplied by perfusion with an oxygen-laden isotonic solution of inorganic salts and dextrose. Blood serum or proteid solutions are not more effective than solutions of common salt—all of which are decidedly inferior in sustaining power to Ringer's solution with sugar. It would seem from this that the sugar solution is effective not so much in washing away fatigue products—the muscle waste—as in supplying a nutrient group. Otherwise, we should expect equally effective results from simple saline perfusion. Within the body as a whole, it is not so easy to analyze the function of the individual non-nitrogenous nutrients in muscular work. To be sure, numerous ergographic experiments seem to demonstrate the effective use of carbohydrates; but the results afforded are not very trustworthy. We have seen that the respiratory quotient varies for the different kinds of materials consumed in the body. A review of the literature suggests that when the body is well supplied with carbohydrates the respiratory quotient remains high during work, indicating a large utilization of carbohydrates. The latter are thus readily used when they are available for the cells of the body; and accordingly the store of glycogen in the muscles is seen to diminish with severe work. On the other hand, metabolism experiments on man fail to indicate any difference in the way the body utilizes the kinetic energy arising from oxidation of the different

nutrients Atwater and Benedict have tested the relative efficiency of fats and carbohydrates by ascertaining whether it costs more energy to do the same work with fats than with isodynamic amounts of carbohydrates. In directly comparable work experiments a somewhat higher efficiency for the carbohydrate than for the fat-diet was observed.

In other experiments not so comparable, less pronounced differences appeared. The general conclusion of the investigators is "that in these experiments the fats were slightly inferior to isodynamic amounts of carbohydrates as a part of a ration for muscular work. But while the natural inference is that calorie for calorie the carbohydrates were slightly superior to the fats as sources of muscular energy, the difference observed was very small and may have been due to some individual peculiarity of the subject with which the more directly comparable experiments were made, rather than to any inherent capacity of the materials to yield energy for external muscular work." Regarding the immediate sources of muscular energy and the character of the substances actually metabolized in the muscles, these experiments give no answer; nor is the solution apparent in the lack of more extensive information respecting the intermediary changes in metabolism.

Other Influences on Metabolism.—Regarding other influences which may be brought to bear upon metabolism aside from the intake of food and muscular exertion, the time has not yet come for any comprehensive summary. The influence of *growth* deserves careful investigation, and a study of the nutritive changes in the young is certain to afford an abundance of practical suggestions. The available data indicate a fairly good absorption of the foodstuffs in young infants, the figures for the total available energy varying from 90 to 96 per cent. of the total intake. Sugar absorption appears to be by far the most perfect. Oppenheimer first called attention to the fact that the gain in weight of infants is directly proportional to the quantity (or calories) of milk ingested. Thus two different children during the second month of their lives gained 191.2 and 201.1 gm. for each kilogram of milk given; in the third month, 120.3 and 138.5 gm.; in the fourth month, 102.6 and 103.3 gm.

It is noteworthy that the appetite determines the regular ingestion of sufficient energy for the life processes, plus a small but fixed extra percentage necessary for growth. Lusk has formulated a law of growth, that in the development of the normal young of the same age and species, a definite percentage of the energy content of the food is retained for growth irrespective of the size of the individual. According to Heubner, vigorous growth in infants demands an intake of energy amounting to 100 to 120 large calories. That growth itself is attended with an active chemical exchange is shown by studies on the respiration of the embryo, in which the gas metabolism has been found to be as active as that of adults. The metabolism of the young appears to be somewhat more active than that of the adult, as far as can be judged from the data on page 688 which the authors have compiled from various sources.

Although it appears as if the metabolic processes are less extensive in *old age*, it must be remembered that the activity of the individual is greatly diminished, and our conclusions are based upon the dietetic habits of the old rather than on actual metabolism experiments. It

seems doubtful if any specific influence of old age aside from diminished muscular exertion can be demonstrated.

AGE OF SUBJECT.	CO ₂ output per kilogram, and per hour.	Urea output per kilogram, and per day.
	<i>Grams.</i>	<i>Grams.</i>
35 years.	0.51	0.5
20 years.	0.53	0.5
15 years.	0.60	0.5
9-13 years.	0.90	0.6
3-7 years.	1.20	0.7

There is no evidence that the *psychical processes*, as exemplified in nervous excitement, specifically influence metabolism. During *sexual changes* modifying influences are doubtless at work, but they lack experimental verification.

More conspicuous than the preceding are the effects which external *climatic* and *hygienic* conditions impose upon metabolism. The explanation for many of these undoubted effects is not yet forthcoming. In some cases, problems of temperature regulation seem to be concerned; for the temperature, relative humidity of the air, and its rate of movement modify the "physical" regulation of the body temperature so long as an excess of heat is produced in metabolism. But below the so-called "critical temperature" (about 37° C. for naked man, according to Rubner, and 15° C. in ordinary clothing) the incidental heat production no longer suffices to maintain the normal temperature of the body, and additional body material must be oxidized for this special purpose. Under ordinary circumstances this is avoided by the devices used to keep our immediate surroundings above the point where a "chemical" or metabolic regulation of temperature is called into play. Herein lies the indirect influence of *clothing* on metabolism. Materials which prevent radiation and conduction of heat, as well as modes of dress which fail in a cold environment to conserve the heat produced by the body, exert an influence on the chemical changes going on in the organism concerned. We are accustomed to dress ourselves in such a manner as to make the loss of heat equivalent to that which the naked body would undergo at about 33° C. The *cold bath*, rapidly removing heat from the body, stimulates katabolism. From calorimetric observations, Rubner has calculated the effects of an hour's bath at various temperatures in terms of *additional fat* katabolized, as follows:

Bath at 15° C.	Katabolism of fat = 52	grams.
Bath at 20° C.	Katabolism of fat = 37	grams.
Bath at 25° C.	Katabolism of fat = 22	grams.
Bath at 30° C.	Katabolism of fat = 9	grams.
Bath at 35° C.	Katabolism of fat = 0.7	grams.

Lately, the action of *high and low altitudes* has received considerable attention in connection with climatotherapy. It appears that both mountain- and sea-air may exert a stimulating influence upon metabolism in those unaccustomed to the climatic condition selected. This is made evident in the increased consumption of oxygen and output of carbon

dioxide at rest without food. It has become quite certain that other climatic factors than the diminished barometric pressure are effective in the case of mountain experiences and similar subtle influences appear to come into evidence at the seashore. Doubtless the direct insolation plays some part in the action of climate at high altitudes; in illustration of this we quote from Rubner the observation that at Davos, on sunshiny days without winds, one can remain quietly seated in the open air at -1° C. without wearing heavy clothes. The vacuum thermometer indicating the degree of insolation may rise to $+43^{\circ}$ C. at the same time. It is not impossible that increase in the radio-activity of the air in mountain regions may exert a physiological influence. In saying this, however, we are still within the realm of conjecture.

FATE OF THE INGESTA AND ORIGIN OF THE EXCRETA.

No review of this subject would be complete without some consideration of the changes which the digested compounds experience in becoming incorporated with the tissues and fluids or transformed into materials for the purposes of movement and vitality and finally altered into products ready for excretion. This *intermediary metabolism* still remains a most obscure chapter; and the progress of physiological chemistry has helped to make the subject more complex. Thus, in speaking of the albuminous substances we are now prepared to distinguish between the various members of a great group of organic compounds related in many chemical and physical features and yet sufficiently different in structure and physiological behavior to demand a special interpretation for their roles in metabolism in many instances. In this way, for example, a familiarity with the specific metabolism of the nucleoproteids, with their phosphorus, carbohydrate, purin, and pyrimidin complexes, has been obtained; and little by little the independent origin of the different nitrogenous excretives has been unraveled. The source of the katabolites, urea, uric acid, and oxalic acid, has been traced to different members of the proteid family; whereas at one time they were attributed to a common source which was assumed to give rise to diverse end-products by obscure variations in the metabolic processes of the organism, now yielding one, now another of them. Similarly, the physiologist is able at present to distinguish between the metabolic fate of proteids which convey phosphorus to the organism and those which do not; or, looking from another point of view, to refer eliminated phosphorus to a variety of possible origins—the phosphates ingested, or the phosphorus of gland nucleoproteids, lecithins, or disintegrating leukocytes, as the circumstances may direct. In this way he aims to obtain a deeper insight into the chain of events which constitute intermediary metabolism—what Foster has termed the “gaps and guesses” of nutrition. There is so much which is uncertain and the subject of controversy that we shall aim to recount briefly only such facts and theories as have received more general acceptance, or are, in our opinion, deserving of special recognition.

Metabolism of Carbohydrates.—Carbohydrates apparently experience the best utilization of all the types of foodstuffs commonly ingested. In the healthy infant, which receives these nutrients in the form of milk-

sugar, no trace of sugar ordinarily escapes with the stools, and in the adult the record is scarcely less satisfactory for the digestible carbohydrates. They are, of course, not all absorbed in the form in which they are ingested. Experimental evidence indicates that the monosaccharides (hexoses and pentoses) are the "physiological" sugars and that the digestible carbohydrates are converted into this form before they are absorbed and utilized. The possibility of functional adaptations of the digestive glands to the materials upon which their secretions are required to act has been suggested in recent years. The experimental evidence thus far presented is, however, unconvincing. To what extent, if at all, such functional adaptations may involve an inter-relation between the diet and certain nutritive factors important in practical experience remains to be learned.

When soluble carbohydrates enter the circulation without intervention of the alimentary digestive processes they are only retained in part, depending on the nature of the compound introduced. The monosaccharides, dextrose and levulose in particular, are not excreted at once; but such carbohydrates as cane-sugar, milk-sugar, glycogen, or dextrins, reappear to a considerable extent in the urine when they enter the blood as such. Maltose (malt-sugar) appears to afford an exception in this respect, presumably owing to the presence of a maltase, or maltose-inverting enzyme in the blood itself. Dextrose may be introduced into the circulation by a variety of channels and is in every case largely retained unless the quantity and rate of introduction are excessive. Under ordinary circumstances in man, the monosaccharide products of digestion are carried in the portal blood-stream to the liver, and doubtless go to form the glycogen store of this and other tissues. So far as is known, the glycogen from different sources is chemically the same.

Aside from glycogen, another important carbohydrate constituent of the body is the blood-sugar. This has repeatedly been identified as dextrose. Whether it exists there in the free state or in combination with other organic groups like the lecithins, or both, has not been answered to the satisfaction of all physiologists. The most recent experimental evidence speaks against the idea of a combination. Two facts deserve emphasis in considering the intermediary metabolism of the carbohydrates; namely, the relatively wide distribution and noteworthy quantities of glycogen which may be present in the body at one time, and the apparent constancy of the sugar-content of the blood. It seems to be demonstrated that there is no pronounced diminution of the percentage of sugar in the blood during starvation, although it is doubtless continually being requisitioned for the needs of the functioning tissues. Neither does work or rest detectably affect the sugar-content of the circulation as a whole; and any condition in which hyper- or hypoglycæmia arises partakes at once of the nature of disease. It is therefore apparent that some regulatory mechanism must be at work in the organism serving to maintain the constant level of the blood-sugar content.

We ask ourselves: How is this constancy maintained? How, on the one hand, is the surplus which the digestive processes furnish retained; and how, despite continued utilization, is the blood replenished with dextrose? Under ordinary circumstances of health, the blood contains about 1 per mille of dextrose. Whenever sugar tends to increase to

any considerable extent beyond this and exceeds the limit of about 3 per mille, dextrose is eliminated by the kidneys. Indeed, it is not unlikely that the intestine may act as an excretory organ at times when the sugar-content of the blood becomes physiologically excessive and the kidneys are insufficient. These processes are normally not called into play; for the excess of carbohydrate is taken care of and retained in the organism or immediately burned up. But when this fails to be effected completely, an excretion of sugar may follow the intake of relatively large quantities of carbohydrate, giving rise to the condition spoken of as "alimentary glycosuria." The failure to retain or destroy the sugar intake may be a relative one in this case and depend upon the quantity poured into the circulation at one time; thus, 100 grams of dextrose ingested in a single dose can ordinarily be retained by a healthy individual, and the failure in this respect is generally regarded as an approach to a pathological condition.

When, however, the monosaccharide sugar is retained in the organism it is not always burned at once. There can be no question regarding the increase of glycogen in the liver following the introduction of some carbohydrates at least. Whatever discussion the glycogenic function of the liver has aroused has been directed at the theory of glycogen deposition. The anhydride theory assumes a chemical re-arrangement and alteration of the sugar molecule when it reaches the liver, together with a polymerization by which the relatively insoluble glycogen is retained in the hepatic cells, ready to be dispensed in ways which will be considered later. A few physiologists have believed that the glycogen is not derived from the carbohydrates ingested; the latter are supposed to be burned up directly, thus sparing the glycogen which they believe is formed from proteid. This is the *sparing* theory. Neither of these theories is satisfactory in explaining the facts of experiment. Nor can the newer *metabolic* theory be said to answer all objections. According to this view, the food-sugars are not converted directly into glycogen, but are first synthesized into the living protoplasm from which in turn glycogen is split off—secreted as it were. The most important feature of such a theory lies in the necessity for proteid in the construction of a glycogen-yielding protoplasm. It makes clear why more glycogen is apparently stored when both proteid and sugar are furnished, and how hexose sugars, with such different configurations as dextrose, levulose, and galactose afford, can yield a carbohydrate of constant chemical structure. The function of glycogen-formation thus becomes a property of the living protoplasm-constructing cell, and the deposition of glycogen in so many tissues of the body as well as in such vegetable cells as yeast can more readily be understood.

Again, the *metabolic* theory of glycogen-formation makes it somewhat easier to appreciate how substances like glycerin or even inorganic salts like ammonium carbonate cause an increase of glycogen in the liver. These compounds afford both glycogen and urea, by inciting a katabolism of the liver protoplasm, which results in the liberation of carbohydrate on the one hand, and nitrogenous groups on the other. The glycerin or ammonium salt accordingly need not be considered as directly entering into the glycogen-yielding process and itself participating in its construction. The metabolic theory also lends probability to the power

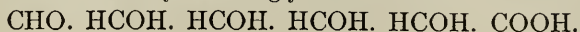
of many, if not all, cellular tissues to produce glycogen as well as the liver, so that the muscles need not be assumed to owe their store to the supply transmitted from the liver. The living protoplasm can rebuild glycogen in any organ; and we can understand how starving animals can in part renew the glycogen-content of their tissues, and why even in prolonged hunger, as Pflüger has shown, the tissues may still contain a noticeable proportion of the carbohydrate. Pflüger, to be sure, is unwilling to admit the formation of glycogen from proteid, and assumes in the case of the starving organism that the glycogen is only slowly used up. Is it not more likely that the proteids incorporated in the indefinite substance called protoplasm may take part, as indicated above, in the renewal of the glycogen in the cell? And with the necessity of both nitrogenous and non-nitrogenous groups admitted for protoplasmic anabolism, it becomes clear that with the lack of *either* of these constructive materials glycogen can be manufactured only at the expense of ready formed protoplasm, involving in turn increased katabolism of nitrogenous material. We might expect in this event that proteid and carbohydrate katabolism should run parallel, or, in case of a failure to use the carbohydrate, its excretion in quantities strictly proportional to the nitrogenous waste—as it is observed in certain pathological conditions—could more easily be understood. For no conclusive evidence of a direct conversion of food proteid into carbohydrate has yet been advanced. Whatever our view regarding the origin of glycogen may be, whether we admit its formation from proteid or sugar alone or from both, directly or indirectly, or even from fat—for which there is much less evidence—the important role of glycogen as a carbohydrate reserve in the body must generally be admitted.

Returning to a consideration of the fate of the ingested carbohydrates in metabolism, we have followed them until, in pathological conditions, they are excreted unused and unchanged or disappear from the circulating media. There remains the second inquiry: How is the sugar-content of the blood maintained and the losses to the tissues made good? Without discussing this point we incline to the view that it arises from glycogen, notably in the liver. The blood-sugar rapidly sinks in quantity when the liver is cut out of the circulation; and it becomes difficult, if not impossible, to produce any typical hyperglycemia by experimental means, when the glycogen-content of the liver has previously been greatly reduced. In the conversion of glycogen into sugar, enzymes are doubtless concerned to an important extent. Soluble ferments capable of inducing such changes are known to exist, and there is no good ground for denying that the processes which can be observed postmortem in the liver go on during life, though perhaps at a greatly altered rate. A reaction of this type is, furthermore, quite in accord with prevailing views regarding the importance of enzymes for the chemical organization of living cells. And in attributing the vital process of sugar-formation to enzyme activity, it is unnecessary to postulate any extra-cellular secretion of the active agent; the modern view merely attempts to define more precisely the character of the chemical reaction involved by classifying it with those transformations known as enzymatic. The relation of the nervous system to these manifold processes is at present ill-defined and only partly understood, although its physiological bearing must be manifest. Finally, it seems likely that glycogen is not used directly, but is previously transformed into sugar.

To be of use to the organism in furnishing energy, the carbohydrate must be burned up. From the standpoint of energy transformations it makes little difference whether it is consumed rapidly and at once, or whether the decomposition goes on more slowly and in successive stages, as is the case in the living organism. To the physiologist, however, these *intermediary* processes are of no little concern; and for the physician they attain due significance in the light which appreciation of them throws upon many obscure pathological states. Experimentally, glycolysis, or sugar destruction, has been found to be characteristic of various tissues as well as of the blood. Undoubtedly, such destructive changes go on in the muscle during activity; but whether the glycolytic power of the muscular tissue is reinforced by contributions from other organs, such as an internal secretion of the pancreas, and whether the chemical reaction involved depends on the presence or absence of sufficient oxygen, cannot be foretold at the present moment. Some investigators believe that the process of carbohydrate utilization in the body is comparable with typical fermentation changes as exhibited in the destruction of sugar by yeast or its zymase; for others the intermediation of oxygen in this internal respiration seems more important. Regarding the nature of the products actually formed, little is definitely known at present; carbon dioxide is undoubtedly produced and various organic acids appear to arise in an intermediate stage. Perhaps we have in this the explanation of the tendency of an active tissue to become more acid when the circulation and oxygen supply are deficient. We regard it as extremely probable that the *paralactic acid* found in the animal organism has its origin in carbohydrates. Ordinarily it is further burned up; but when there is a lack of oxygen we have to deal with an incomplete combustion of the lactic acid derived by cleavage from sugar, without denying the *possibility* of a similar production from proteids.

In accordance with this view, a considerable excretion of lactic acid and sugar is found in poisoning with carbon monoxide, in which an oxygen deficiency is always manifested; and simultaneously with the formation of lactic acid a decrease in the glycogen reserve is noted. Another evidence of the inter-relationship between lactic acid and carbohydrate katabolism has been offered in cases of phosphorus poisoning. Here the urine contains paralactic acid; but when artificial diabetes is produced by means of phlorizin during phosphorus poisoning, the lactic acid disappears from the blood and urine with the appearance of the sugar produced by the phlorizin. According to Mandel and Lusk, this indicates that "lactic acid produced from the cleavage and denitrogenization of proteid, whether this occurs in the intestinal wall or in the liver or elsewhere, is first synthesized to dextrose within the organism (liver) before further distribution to the tissues. In the case of simple phosphorus poisoning this distribution of dextrose takes place with resultant anaërobic cleavage, leading to a second production of lactic acid." Following the view of Hoppe-Seyler, the formation of lactic acid from carbohydrates and its elimination may be regarded as an abnormal process, occurring only under the imperfect physiological conditions attending an insufficient supply of oxygen.

Another compound which doubtless owes its origin to the intermediary metabolism of the carbohydrates is glycuronic acid



This is readily obtained in the urine paired with camphor, thymol, menthol, and a large number of other compounds when the latter or related antecedents are introduced into the body. Conjugated glycuronates are found in traces in the blood and liver; and the normal urine is said to contain very small quantities in combination with phenol, cresol, indoxyl and skatoxyl. The possibility of a formation of glycuronic acid from proteids cannot be denied at present and the problem is associated with the broader question of sugar formation from proteids. But the available evidence points to carbohydrates as the chief, if not the only, source of this agent with which toxic compounds become conjugated and excreted in less harmful forms. Animals which have been starved sufficiently long to diminish to a minimum their carbohydrate reserve (glycogen) yield little, if any, glycuronate after ingestion of camphor. Conversely, the toxic action of some of the conjugated compounds can be greatly diminished by feeding carbohydrates which yield glycogen or dextrose in metabolism.

The glycuronic acid conjugation appears to take place in the liver, and the primary significance of its formation, therefore, probably lies in its antitoxic action. This is a well-known function of metabolic products of the proteids as we see it exemplified in the formation of ethereal sulphates. In cases such as profound cocaine intoxication, where dyspnoic conditions arise, glycuronates have been found in increased quantity in the urine. P. Mayer believes that, normally, the oxidation of dextrose in the body proceeds through the stage of glycuronic acid, and that when further katabolism is checked the imperfectly oxidized carbohydrate is eliminated in part in this form. Corresponding with this view, a simultaneous elimination of both glycuronates and sugar is observed under pathological conditions in which circulatory and respiratory disturbances play a part. A further step in the oxidative degradation of sugar is oxalic acid, which may likewise escape unburned under certain conditions. It is not uncommon to find oxaluria and glycuronic acid elimination associated in diabetes.

Considering the preceding facts, it would appear as if carbohydrates may undergo fermentative decompositions in the body, or be decomposed through a succession of oxidative changes. Under conditions of imperfect oxidation one or more of these *intermediate* products may escape from the body. Glycosuria is thus only one evidence of a defective intermediary metabolism of the sugars. Glycuronic acid, saccharic acid, oxalic acid, lactic acid, and, perhaps, other organic acids primarily associated with diabetes are referable to the same source. Such a view may at any rate serve toward the construction of a tentative theory of intermediary carbohydrate metabolism.

Reference may be made to other less frequent anomalies of carbohydrate metabolism, such as pentosuria, levulosuria, lactosuria, and galactosuria. The excretion of lactose (milk-sugar), during and after pregnancy, is a temporary disturbance referable to an escape of the carbohydrates from the active mammary glands into the circulation. When these glands are extirpated, lactosuria is never observed. The excretion of levulose has been frequently reported and seems to occur in conjunction with dextrose elimination in many diabetics. The fact that dextrose can be converted in part into levulose in alkaline media makes this less difficult of interpretation. Galactose has been found in the

urine of infants suffering with gastro-intestinal disorders. (Langstein and Steinitz.) It represents an unutilized inversion product of milk-sugar absorbed from the intestine of milk-fed individuals. In explanation of the phenomena of pentosuria little can be said at present. The ordinary diet of man contains pentosans, which yield five-carbon sugars ($C_5H_{10}O_6$), such as xylose and arabinose, on hydrolysis. When pentoses are fed they are in part oxidized. It is unlikely, however, that the sugar eliminated in chronic pentosuria is derived from the food, since the elimination continues even during starvation. The nucleoproteids such as are found in the pancreas also yield pentose; but the latter is l-xylose, whereas the urine pentose appears to be r-arabinose. Ordinarily, there is no interference with the oxidation of the hexoses in pentosuria; and the condition may persist for years without exhibiting any other untoward symptoms. For the present, pentosuria is of interest chiefly as an illustration of a curious and unexplained anomaly of carbohydrate metabolism.

Metabolism of Fats.—In presenting a review of the present knowledge regarding the metabolism of fats, we shall be obliged to touch upon many topics which are still the subject of controversy. The views expressed are not to be interpreted too rigidly, for dogmatic statements should not be expected in a department of study which is at present being pursued by many investigators. An adult man can digest 300 grams of fat per day, provided that it is offered in suitable form. What becomes of this after it leaves the alimentary tract? Furthermore we may inquire whether the tissue fat is derived directly from the ingesta or synthesized in indirect ways, and what are the chemical processes which inaugurate these transformations?

At the outset, the radical changes which prevalent ideas of fat digestion and absorption have experienced should be mentioned. A few years ago it was thought that fats were absorbed in the form of an emulsion, the undissolved and finely divided particles passing through the epithelial cells in some mysterious manner. This view has been altered more recently; for we have learned of the more extensive distribution of lipolytic enzymes in the alimentary tract, the process of fat cleavage apparently having a beginning in the stomach itself. Fatty acids and soluble soaps are formed in not inconsiderable quantities in the digestive tube. Furthermore, bile affords a medium for the solution of large quantities of free fatty acids at the temperature of the body. It is difficult to obtain indisputable evidence of the absorption of unchanged fat, except by histological methods which are perhaps not wholly reliable. Certainly other insoluble substances (such as fluid paraffin) are not absorbed even when they are finely emulsified, but are recovered *in toto* in the feces. While it is perhaps too soon to say that fats must be completely transformed by digestive change to soluble forms before they can be absorbed, it seems certain that such a preliminary cleavage or saponification does take place to a degree not formerly appreciated. Once beyond the lumen of the gut, the fragments are again synthesized to neutral fats. Foreign esters of the fatty acids reappear as glyceryl esters. There is some evidence that the lymphatic tissue-elements are concerned in these synthetic transformations.

When fats reach the blood-stream through the lymph channels, they are exposed to a peculiar metamorphosis which is still little understood. The

suspended particles of the minute emulsion of the blood-fats may become changed into soluble and diffusible substance. Perhaps it is in this intermediary soluble form that fats are transported to the tissues, as we know carbohydrates to be. Regarding the nature of the processes a few definite statements may be ventured. The transformation is inaugurated by some constituent element of the erythrocytes which is destroyed by high temperatures; thus the change partakes of the nature of an enzyme reaction. It does not go on in the absence of oxygen, yet the chemical change certainly is not one of complete oxidation. The resultant product, unlike the original fat, is insoluble in ether and soluble in water. Neither is this fat metamorphosis a lipolytic change of the usual digestive type, comparable with the cleavage produced by ordinary lipases. The latter appear to be almost completely wanting in the blood; the various body tissues are, on the other hand, supplied with more or less lipolytic power, so that we may postulate a widespread distribution of lipase in the animal body. The reversible action of fat-splitting enzymes, *i. e.*, the capacity of the same enzyme solution to synthesize neutral fats from fatty acids and alcohols, as well as to effect a corresponding cleavage of neutral fats, has directed attention to the probable important role of lipases in the tissue metabolism of fats. It is not unlikely, therefore, that the reserve supply of tissue fats is in some way transformed into more soluble forms by enzymes precisely as the storage glycogen may be, and thus transported from the tissue cells; while the deposition of transported fat components is perhaps accomplished by a synthesis in which enzymes are likewise effective agents. Other esters are similarly attacked by tissue lipases. Enough has been said to indicate the actual occurrence of synthetic, lipolytic, and solvent enzymes for the fats. Connstein has offered the following tentative description of the immediate fate of food-fats. When ingested in the form of an emulsion, they may be in part hydrolyzed in the stomach; otherwise the lipolysis begins in the intestine. The cleavage products are absorbed and incidentally resynthesized to neutral fat, which reaches the blood through the chyle. In the circulation, the fat is transformed into an (at present unknown) soluble and diffusible modification which can readily pass through the capillaries, and thus gain direct access to the tissues themselves where a regeneration of fat goes on. When the fat depots in the tissues are drawn upon, lipolysis again takes place. Before accepting this it remains to be seen whether the emulsified particles of fat cannot pass through the walls of the capillary vessels in other than water soluble forms. The possible fat-dissolving power of the lipoids (lecithins, etc.) present in all cells is not to be overlooked in this connection. The inadequacy of our present knowledge is only too patent.

The fat which enters the circulation is not unlikely in part involved very soon in the combustions continually going on. Where this katabolic change occurs can only be surmised; the liver is suggested, although the evidence is somewhat indirect. In greater part, the fat is undoubtedly first deposited, the most important depots being the subcutaneous connective tissue, the liver, and the folds of the peritoneum. The panniculus adiposus is of foremost importance in fat deposition, the other storage places being utilized prominently only when the former has already been well taxed. The liver may become the seat of transitory or temporary storage. There exists in the liver a kind of antagonistic relation between

glycogen and fat, as the result of which fat fails to accumulate in the liver so long as glycogen is abundantly formed there and the other fat depots are available. Thus it happens, as Rosenfeld has pointed out, that the livers of fattened pigs are frequently poor in fat, owing to their richness in glycogen; whereas those animals like fishes, which live on diets poor in carbohydrates (glycogen-formers) store up enormous quantities of fat in their hepatic cells. In man, with whom a mixed diet is customary, fatty liver is normally not observed for reasons just advanced. Lusk has pictured conditions when, owing to diabetes, or activity of the mammary gland in utilizing dextrose to form milk-sugar, the cells affected become "sugar-hungry cells," which attract fat in greater quantity than they can burn it (fat infiltration).

The preceding remarks involve the assumption that tissue-fats may owe their origin directly to the food-fat, and lead to the broad question of fat-formation in the animal body. Such an assumption is more easily made in the case of fats because they are believed to undergo less radical changes in the process of digestion than do carbohydrates or proteids, and the re-synthesis occurs in the passage through the absorbing cells. Kassowitz has modified the point of view somewhat by regarding the chyle-fat as a product of the internal secretion of the intestinal epithelial cells. From his standpoint the make-up of the circulating fat which is able to gain its way to the fat depots is dependent upon the protoplasmic activity of these living cells, a view which implies a somewhat indirect deposition of the fat ingested. Such distinctions, however, are verbal rather than real. The important facts are, firstly, that when foreign fats possessing recognizable chemical and physical characteristics are fed, the constituent fatty-acid group which lends peculiar character to them can be detected in the tissue-fats. The subject has attained importance in agriculture where the quality of the fat in animals is a matter of serious commercial moment. In the second place, it is noteworthy that despite variations in the character of the fat fed, there is an inherent tendency to maintain a typical constancy for the species and the particular depot under consideration. Mutton-fat differs from the fat of cattle even under somewhat similar conditions of diet; and in the same animal the fat has not the same composition in different parts of the body. These facts mean that various factors are at work in determining the make-up of the adipose tissue, and especially suggest other sources for body-fat besides the fat ingested. Among these, carbohydrates are without question the most important. The feeding of a diet rich in carbohydrate is a familiar method of fattening animals. It does not, however, afford rigorous proof of the origin of the fat produced, since every dietary of this sort usually contains an abundance of proteid. In the formation of milk-fat we have a specific illustration of the relation of carbohydrates to fat formation. Jordan fed a cow during ninety-five days on a ration from which the fats had been nearly all extracted, and the animal continued to secrete milk similar to that produced when she was fed on the same kinds of grain and hay in their normal condition. The yield of milk-fat during the ninety-five days was 62.9 pounds. The food-fat eaten during this time was 11.6 pounds, of which only 5.7 were absorbed; consequently at least 52.7 pounds of the milk-fat must have had some source other than the food-fat.

The milk-fat in the above experiment could not have come from previously stored body-fat. This is supported by three considerations: (1) The cow's body could have contained scarcely more than 60 pounds of fat at the beginning of the experiment; (2) she gained 47 pounds in weight during this period of time with no increase of body nitrogen, and was judged to be a much fatter cow at the end; (3) the formation of this quantity of milk-fat from the body-fat would have caused a marked condition of emaciation, which, because of an increase in the body weight, would have required the improbable increase in the body of 104 pounds of water and intestinal contents. During fifty-nine consecutive days, 38.8 pounds of milk-fat were secreted and the urine nitrogen was equivalent to 33.3 pounds of protein. According to any accepted method of interpretation, not over 17 pounds of fat could have been produced from this amount of assimilated protein. From these considerations, it is concluded that the milk-fat was produced in part at least from carbohydrates, as we know to be the case with body-fat.

The determination of the place where the conversion of carbohydrate to fat occurs is not easy. One is tempted to refer it to those places where carbohydrates accumulate, *viz.*, the liver and muscles. But it is not less likely to be perfected in those locations where fat is deposited—in the cells of the subcutaneous adipose tissue, for example.

With reference to proteids as fat-forming elements, it is impossible to make any conclusive statement at present; the evidence is by no means convincing and there is a growing tendency to regard such a process as unlikely, if not impossible. In this respect, the theory of fat-formation has been seriously modified in recent years, as the outcome of the controversy between the adherents of Voit and of Pflüger. Even pathological fat-formation, typically described as "fatty degeneration" is now for the most part explained as a "fatty infiltration," *i.e.*, the introduction of fat transported from fat-depots to the "degenerated" tissue. Corresponding with this view, Rosenfeld and others have removed from "fatty" livers of dogs previously fed abundantly on some recognizable foreign fat and then poisoned with phosphorus, the characteristic foreign fat fed. The "degeneration" fat is in these cases not manufactured from the cell protoplasm, but transported and infiltrated. Accordingly, further, the total fat-content of animals poisoned with phosphorus, which induces the typical symptoms of so-called fatty degeneration of the liver, is not increased, although its distribution between the various tissues is changed. Recent studies on the distribution of fat in pathological conditions, have shown that the impressions gained by mere microscopic examinations may be utterly misleading, as the fats are frequently incorporated very intimately in the tissues.

In attempting to offer an explanation of the fatty metamorphosis in cells subject to toxic influences, we quote from Rosenfeld, the champion of the infiltration theory: When the proteid content of the cell is attacked by any noxious agency, certain molecules of the protoplasm are thrown out of function. In order to maintain its vitality, the cell now obtains its energy in the oxidation of all the carbohydrates which it controls (hence the liver soon becomes glycogen-free) or when this is impossible the proteid content is enriched by importation of proteid. Accordingly it is observed that in many intoxications, as with phosphorus and alcohol, the proteid content

of the liver is increased. But when these various sparing agents are no longer available in sufficient quantity, the cell seeks the last help by attempting to recoup its losses with fat abstracted from the circulating blood which is in turn replenished from the fat-storage depots. With this infiltration of fat into the cell, the latter may succeed in maintaining itself and its energy transformation until the toxic effects have disappeared; if not, the infiltration is succeeded by a true degeneration and the cell dies.

Referring to the peculiar aspect of fat-metabolism afforded in the formation of milk-fat, we have already noted that the latter may, in the absence of an abundant fat-supply, be formed from carbohydrates. Under usual conditions, the fat of the milk is partly derived from the body-fat, but chiefly from the fat of the food. The fat is probably not transmitted directly from the blood, but is modified in the secreting cells of the mammary gland. If for any reason the quality of the milk is changed, there is always a tendency to return to the normal. The composition of the butter-fat is modified within narrow limits by the fat of the food; but the percentage of butter-fat in milk is very little influenced by foods containing a large percentage of oil, or even by albuminous foods. Breeding rather than feeding seems to play the important part in determining the quantity and quality of the milk; the fact that foreign fats do pass into the milk is, however, not to be overlooked and corresponds with the newer findings regarding the ready transportation of fat in the body from one depot to another. There is also some evidence in the case of the sebaceous glands tending to show an alteration in the make-up of their fatty secretion, depending upon the character of the fat fed.

During embryonic growth, a consumption, rather than synthesis or deposition of fat, occurs in so far as can be judged from experiments on species which have an extra-uterine development. Thus a marked loss of fat is noted in the chick embryo during the process of development. The fresh egg containing 5.4 grams of fat may show a diminution to 2.7 grams or less.

In connection with fats, reference may be made to a group of compounds widely distributed in the body in all types of tissues and resembling fats in various ways. The lecithins, cholesterin and its esters, cephalins, and cerebrins, may be considered briefly under the general term of "lipoids" or fat-like compounds, which differ widely among themselves, but possess the general physical properties and solubilities of fats. They are especially prominent in the nervous tissues, and their behavior toward the volatile anæsthetics is made the basis of the Meyer-Overton theory of narcosis. Of the metabolism of these substances, little can be said. Lecithins disappear from the cells far less readily than do the ordinary fats; their content is far more constant so that they appear to be an integral part of the protoplasm. In the disintegration of nervous structures, decomposition products of lecithin (cholin, glycerylphosphoric acid) appear to be liberated, as well as in certain autolytic changes. For the present, it is scarcely profitable to do more than point out the possible physiological significance of the lipoids in the work of the cells. Regarding their origin little is known.

Of the stages through which fats pass in their katabolism to the end-products, water and carbon dioxide, very little has been ascertained. As in the metabolism of carbohydrates, pathology has shed some light. In

severe diabetes, where carbohydrates are not burned up, fats are drawn upon. In this condition, as also in inanition, the "acetone bodies" may be eliminated in considerable quantity. This is not true under ordinary conditions on a mixed diet. The compounds formed in the intermediary metabolism of fats under these conditions of imperfect combustion are acetone, aceto-acetic acid and β -oxybutyric acid.

Formerly, these compounds were attributed to the proteids; but at present, they are generally associated with metabolism of the fats, and presumably represent products of the incomplete oxidation of higher fatty acids. In health, and on the customary mixed diets, only a few milligrams of acetone are excreted daily. In hunger, the quantity may increase to over a gram per day. Carbohydrates (and perhaps alcohol) check this production at once, but not proteids or fats. In diabetes, we have the extreme case in which figures somewhat as follows have been observed: Acetone, 15 grams; aceto-acetic acid, 26 grams; β -oxybutyric acid, 102 grams per day. It may be, as Fr. Müller has suggested, that the normal metabolism of fats, *i. e.*, oxidation of the higher fatty acids to carbon dioxide and water, goes on perfectly only when a certain proportion of sugar is simultaneously burned up, in the failure of which oxybutyric and aceto-acetic acids arise as intermediary products which cannot be completely burned up. Whether the chemical abnormality hinges on the formation of these compounds or on the inability to oxidize them is uncertain. Accordingly, it is at present impossible to say whether they represent intermediary stages in the normal combustion of fats or not.

Corpulence is scarcely to be regarded as a pathological manifestation of fat metabolism. Direct observations have failed to indicate any diminished capacity of the organism to burn the deposited fats. We have rather to deal with a disproportionate relation between intake of food and food utilization. Whatever apparent diminution in energy transformation may occur is attributable primarily to the relative muscular inactivity of corpulent individuals. A small daily excess may lead to a considerable accumulation of body-fat. Finally, all influences which diminish the combustion processes in the body favor corpulence; these include lack of muscular exertion, sleep, and conservation of body-heat. Some idea of the quantities of fat which may be retained in corpulency is afforded by observations of Meyer and Falta. In a person of 111 kilograms body weight, the thoracic and abdominal cavities furnished 9 kilograms of fat-tissue, the subcutaneous tissue 27 kilograms. These 36 kilograms corresponded to 30.2 kilograms of pure fat. The muscles were estimated to contain an additional 13 kilograms, so that the entire body yielded 51 kilograms of fat or 38 per cent. of the total weight.

Metabolism of Proteids.—The characteristic products of proteid katabolism are found in predominant quantity in the urine, although the fæces and sweat also contain part of the nitrogenous waste. In addition to urea, creatin, creatinin, uric acid and other purin derivatives, hippuric acid, and ammonium salts, a few others occur in quantities which are normally very small but may be largely increased when metabolism is disordered. The sulphuric and phosphoric acids eliminated in combination with various bases are also for the most part referable in origin to the proteids which contain sulphur and phosphorus. The

chemical nature of the nitrogenous metabolic products which escape with the stools is scarcely known; the small portions lost with the sweat are allied closely to those found in the urine.

In following the transformations of proteids in the organism, it is necessary to bear in mind that they represent a great group of foodstuffs varied in physical characters and chemical behavior, yet essentially allied in structure in so far as they yield similar decomposition products. The latter are generally comparable, whether produced by hydrolysis with acids or by cleavage with proteolytic enzymes. The simpler types of proteid subjected to such decomposition yield leucin, glycocoll, α -amino-valerianic acid, alanin, aspartic acid, glutamic acid, serin, cystin, tyrosin, phenylalanin, pyrrolidin carbonic acid (prolin), oxypyrrolidin carbonic acid, lysin, arginin, histidin, tryptophan, and ammonia.

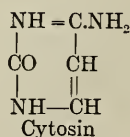
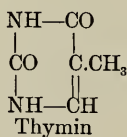
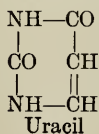
The individual groups of proteids differ in the proportions of these different derivatives and future investigation will doubtless afford additions. From the chemical standpoint, it will be noted that the products thus far obtained are for the most part amino-acids or similar compounds, a preponderance of NH_2 groups in some of them giving a decidedly basic character to the molecule. The conspicuous feature of the

structure of all these derivatives is the presence of the group— $\begin{array}{c} \text{H} \\ | \\ \text{C}-\text{NH}_2 \\ | \\ \text{COOH} \end{array}$

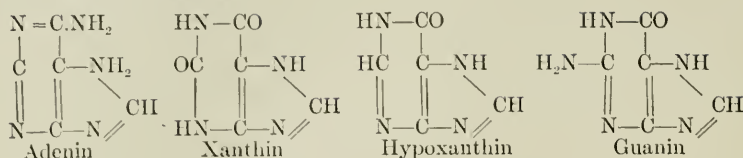
and Fischer has shown that such groups are prone to form continuous syntheses in which the carboxyl group of one becomes united with the amino group of another. This explains the characteristic cleavage of the proteids into α -amino acids and their corresponding behavior toward enzymes as well as their characteristic deportment like acids and bases simultaneously. The sulphur is largely, if not entirely, grouped in the form represented in the cleavage product, cystin; and this throws light upon the origin of the cystin which is excreted in the rare metabolic disturbance connected with cystinuria. Many proteids apparently contain a carbohydrate group; but the typical carbohydrate derivatives obtained from the compound proteids like the mucoids are now recognized as amino-sugars, of which glycosamine is the most common. Other proteids, like the vitellin of egg-yolk and casein of milk, contain phosphorus in radicals not yet recognized by the chemist. This element plays an important part in nutrition, and the phosphorized proteids may thus become responsible in no small degree for the phosphates eliminated. In nucleoproteids, the presence of the nucleic-acid group introduces a new series of complexes which have a significant role. The cleavage products of the nucleic acids include—

1. Phosphoric acid:

2. Pyrimidin derivatives:



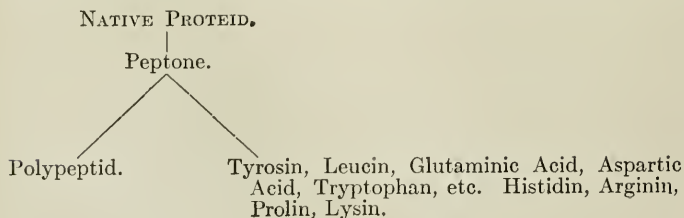
3. Purin derivatives:

4. Pentoses $\text{C}_5\text{H}_{10}\text{O}_5$.

5. Levulinic Acid.

The ferruginous proteids like the hæmoglobins, as well as the albuminoids (scleroproteins) gelatine, elastin, etc.,—all offer specific differences. The reader is referred to the text-books of physiological chemistry for a detailed study of their chemical peculiarities. Enough has been indicated to make clear the possibility of very different nitrogenous transformations, in accord with the varying complexity and chemical make-up of the specific proteids attacked.

In following the ingested proteids we are at once confronted with the question as to how far they are altered by the digestive changes in the alimentary canal before absorption. In respect to this, the views of physiologists have been altered most distinctly in recent years. So long as proteoses and peptones were recognized as the *essential* end-products of digestive proteolysis, attention was particularly directed to the fate of these products in absorption. Inasmuch as they were found to disappear quickly in contact with the intestinal mucosa, while the blood stream beyond was apparently free from them, it was naturally concluded that they are regenerated to native proteid in their passage through the living intestinal wall. Such a view has, however, been rendered untenable by the discovery that proteids can be and presumably are broken down far more completely in the process of digestion than was formerly assumed; and furthermore, it has been found that the disappearance of peptones in contact with the intestinal mucosa is in reality due to a digestive cleavage to non-proteid nitrogenous derivatives through the agency of the enzyme *crepsin*. Whether proteids are ordinarily completely disintegrated in the process of digestion into compounds which no longer give the typical proteid (biuret) reactions before absorption occurs, or whether even the more complex derivatives such as peptones normally traverse the intestinal wall, cannot be decided conclusively from the evidence at hand. It seems unlikely that the proteid derivatives circulate in the blood stream in anything more than traces; otherwise, they would not have escaped detection so often. Tentatively, we may picture the digestive change as occurring in accord with the following scheme, which represents the results of recent experimental observations (Abderhalden):



The polypeptids represent intermediate products, and the controversial features of the question centre in the extent to which digestive cleavage actually occurs in the gut. The determination of the fate of the proteid products—whatever they may be—after they leave the lumen of the digestive tube is attended with even greater difficulties. In the absence of convincing proof of the proteid “fragments” in the portal blood, it has been natural to assume a “regeneration” of the proteid in the intestinal structures. At the present time, however, the occurrence of proteoses and further disintegration products of proteids in the blood, especially after meals, is not at all unlikely. It is less difficult to appreciate how a few types of circulating proteids can be constructed from the ultimate cleavage products of the proteids than from such different complexes as must exist in the diverse proteids of the food. In other words, it is easier to understand how flesh-, or milk-, or wheat-proteids can give rise to the same serum albumin or muscle globulin if they are first broken down to simple fragments which enter into the composition of all the proteids, though in varying proportions. From the teleological standpoint, however, it is not apparent why a *complete* break-down of proteids should occur, only to be followed by immediate resynthesis. It is more reasonable to assume a cleavage into larger nuclei only, which might serve equally well in the anabolic disposition of the nitrogenous materials.

The unsolved problems which have arisen in the study of this first step in proteid assimilation have been thus broadly presented because it is impossible at present to form anything like a satisfactory hypothesis of changes which actually take place. It is by no means certain that only “regenerated” proteid reaches the blood current from the intestinal sources; and it may be found that the quantities of cleavage products absorbed at ordinary intervals escape detection by the methods now available. The increase of ammonia nitrogen in the portal blood during digestion implies an increase in the non-proteid nitrogen of the blood, but the failure to demonstrate it may be ascribed to unfavorable conditions or inaccurate technique. The constancy of composition of the systemic blood in respect to its proteids is as striking as is its fixed sugar-content; and the intervention of the liver in some regulatory or regenerative function is at once brought to mind.

Nor are we better instructed with regard to the further intermediary metabolism of the nitrogenous compounds. We have pointed out the conspicuous behavior of the proteids in their failure, under ordinary conditions of diet and health, to be retained. The elimination of nitrogen begins to increase almost immediately after a meal rich in proteids. Experiments by Sherman and Hawk illustrate the character of this response. When lean beef sufficient to furnish about 64 grams of extra proteid was taken with breakfast, the nitrogen in the urine began to rise in the first three hours and reached a maximum between the sixth and ninth hours, after which it declined at first rapidly and then more slowly. The increased excretion of sulphates was proportional to that of the nitrogen and followed the same general course. It is interesting to note further that the increased heat of combustion of the urine was but little greater than would correspond to an amount of urea equivalent to the extra nitrogen eliminated. The other constituents of the urine

were therefore but little affected, and a moderate gain or loss of body nitrogen did not seem to affect the changes noted.

Falta has observed that after the ingestion of equal quantities of nitrogen in the form of different proteid substances such as egg albumin, casein, gelatin, etc., the *rate* at which nitrogenous equilibrium is again established varies with the materials used. It is not improbable that these differences in rapidity of katabolism are ascribable to an unlike resistance of the proteids to the alimentary digestive processes, which accordingly alters their rate of absorption.

Theories of Proteid Metabolism.—In any attempt at a theory of proteid katabolism, certain fundamental observations must be borne in mind; namely, that this process never stops in the animal body, and that the adult organism has the capacity of rapidly adapting its proteid katabolism to the extent of proteid supply. According to Voit, a distinction must be drawn between the *organized*, or *tissue* proteid, which constitutes an essential part of the living bioplasm, and the *circulating* proteid representing the variable store of rapidly metabolized proteid transported in the blood and lymph stream and temporarily located in the interstices of the tissues and independent of the living substance. The organized proteid is replenished only to a slight degree by the proteid intake, since only a small part of this living bioplasm undergoes destruction under ordinary circumstances. The circulating proteid, on the other hand, is readily disintegrated to the extent that it is not drawn upon for tissue construction and its nitrogenous groups are speedily eliminated. Such a distinction becomes plausible in consideration of the rapid metamorphosis of proteid when a large supply is taken in, the assumption of a previous incorporation into some organic structure and immediate degradation being rendered unnecessary thereby. As Hammarsten has expressed it: The tissue elements constitute an apparatus of relatively stable nature which has the power of taking proteids from the fluid bathing the tissues and appropriating them, while their own proteids, the tissue proteids, are ordinarily katabolized to only a small extent. By an increased supply of proteids, the activity of the cells and their ability to decompose nutritive proteids is also increased to a certain degree. When nitrogenous equilibrium is obtained after an increased supply of proteids, it denotes that the decomposing power of the cells for proteids has increased, so that the same quantity of proteids is metabolized as is supplied to the body. If proteid metabolism is decreased by the simultaneous administration of other non-nitrogenous foods, a part of the circulating proteids may have time to become fixed and organized by the tissues, and in this way the mass of flesh of the body increases. During starvation, or with a lack of proteids in the food, the reverse takes place; for a part of the tissue proteids is converted into circulating proteids which are metabolized, and in this case the flesh of the body decreases. The most essential part of Voit's theory is the supposition that the food proteid of the cells is more easily destroyed than the organized or true protoplasmic proteid.

Pflüger contends that it is only organized proteid which can undergo metabolic transformation—that the circulating proteid must be constructed into tissue proteid or bioplasm before it can take part in the oxidation or katabolism characteristic for proteids. It is the state of

nutrition of the body cells, rather than the circulating proteid which determines the extent of proteid katabolism, a view which is in a way merely a modification of the older theory of Liebig.

The theory of Voit owed its formulation to the inadequacy of the older views of Liebig, which assumed that proteid katabolism must be proportional to muscular activity. Voit believes that the living substance is scarcely, if at all, disintegrated in such cases when the nutritive conditions are satisfactory. The greater part of the excreted nitrogen is accordingly derived from destroyed food proteid. The rapidity with which metabolic changes in proteids occur in the body, and the large amount of such metabolism which may take place when excess of proteid is taken with the food, renders unlikely the previous construction of the latter into living matter. Pflüger's contention regarding the importance of the muscle cell is based upon the experiments of Schöndorff, who observed that the extent of urea formation in the muscles and livers of dogs depends upon the nutritive condition of these cells rather than upon the character of the blood circulating through them. The experimental data are, however, by no means convincing and have lately received adverse criticism.

Kassowitz has advanced a modified conception of proteid metabolism based upon his view that all true foodstuffs are constructed into protoplasm prior to utilization. Carbohydrates and proteids together enter into the composition of the living material, which in turn can split off glycogen or nitrogenous residues no longer assimilable and accordingly excreted. This view differs essentially from Pflüger's, in demanding non-nitrogenous as well as nitrogenous components for the constructive feature. Kassowitz remarks that if food proteid can be "organized" directly and alone, it is not easy to understand the difficulty in putting on flesh when large quantities of proteid are fed without any non-nitrogenous foodstuffs, whereas this synthesis is accomplished far more effectually with less proteid, when sugar is simultaneously available. According to him the excretion of nitrogen has a twofold source, namely, an "active" protoplasmic katabolism, inaugurated by nervous stimulation and affording little of the nitrogenous excretives; and an "inactive" destruction yielding certain reserve products, together with a large part of the nitrogenous fragments now in a form no longer capable of assimilation. There is, from this standpoint, no *luxus* consumption of proteid and no direct decomposition of surplus food proteid, but rather a *luxus* production of protoplasm which in turn suffers an "inactive" degradation and eliminates its nitrogen. Thus it is that, in a full grown and well nourished organism, every increase in proteid supply is followed by a corresponding increase in nitrogen excretion.

Such a view, following closely the standpoint of Pflüger, involves much that is purely hypothetical, and touches closely upon the question as to what constitutes a true food. If we carry the contention of Kassowitz to its extreme, then no toxic substance can ever act as a true food; for toxic action implies protoplasmic destruction, whereas nutritive properties involve some participation in the construction of the protoplasm. If the calories furnished by a substance like alcohol are merely converted into heat, which only serves to increase the useless excess already present—if they can in no wise participate in the liberation of energy as mechan-

ical work because the alcohol is incapable of incorporation in the contractile protoplasm, the real food value of such a compound may be questioned. There are many substances, such as lactic acid, butyric acid, uric acid, etc., which are certainly oxidized in the body. We are not prepared to accept the view, however, that the result of their metabolism is solely a liberation of waste heat; at any rate the question as to the nutritive value of compounds which unquestionably liberate energy in their transformations in the body seems debatable still.

Folin has recently made extensive and careful analyses of the urines of healthy persons living on diets in which the proteid intake was varied within wide limits. This range in the daily output in the same person is shown in the following table:

	July 13.	July 20.
Volume of urine.....	1170. cc.	385. cc.
Total nitrogen.....	16.8 grams.	3.60 grams.
Urea nitrogen.....	14.70 = 87.5 per cent.	2.20 = 61.7 per cent.
Ammonia nitrogen.....	0.49 = 3.0 " "	0.42 = 11.3 " "
Uric acid nitrogen.....	0.18 = 1.1 " "	0.09 = 2.5 " "
Creatinin nitrogen.....	0.58 = 3.6 " "	0.60 = 17.2 " "
Undetermined nitrogen....	0.85 = 4.9 " "	0.27 = 7.3 " "
Total SO ₃	3.64 " "	0.76 " "
Inorganic SO ₃	3.27 = 90.0 " "	0.46 = 60.5 " "
Ethereal SO ₃	0.19 = 5.2 " "	0.10 = 13.2 " "
Neutral SO ₃	0.18 = 4.8 " "	0.20 = 26.3 " "

The diet during the period in which the urine of July 20 was collected consisted of pure starch and cream, so that the intake of proteid was minimal though the quantity of food was considerable. The striking feature is the pronounced change in the distribution of the urinary nitrogen and sulphur, the characteristic end-products of proteid katabolism. For example, the relative proportion of nitrogen eliminated in the form of urea is greatly diminished in the absence of proteid feeding, while the output of creatinin is absolutely unchanged, the relative quantity being greatly increased. In discussing the bearing of these facts, we shall quote freely from the papers of Folin. To explain such changes, it seems necessary to assume that proteid katabolism is of two kinds, which are essentially independent and quite different. The one kind, extremely variable in quantity, yields chiefly urea and inorganic sulphates, no creatinin and probably no neutral sulphur. The other, the constant katabolism, is largely represented by creatinin and neutral sulphur, and to a less extent by uric acid and ethereal sulphates. The more the total katabolism is reduced, the more prominent become these representatives of the constant katabolism, the less prominent become the two chief representatives of the variable katabolism.

If there are two distinct forms of proteid metabolism represented by two different sets of waste products, it becomes important to determine, if possible, the nature and significance of each. The fact that the creatinin elimination is not diminished, when practically no protein is furnished with the food, and that the elimination of some of the other constituents is only slightly reduced, shows why a certain amount of proteid must be furnished with the food if nitrogen equilibrium is to be maintained. It is clear that the metabolic processes resulting in the end-products which tend to be constant in quantity appear to be indis-

pensable for the continuation of life; or those metabolic processes probably constitute an essential part of the activity which distinguishes living cells from dead ones. Folin, therefore, calls the proteid metabolism which tends to be constant, *tissue* metabolism or *endogenous* metabolism, and the other variable proteid metabolism, *exogenous* or *intermediary* metabolism.

The endogenous metabolism sets a limit to the lowest level of nitrogen equilibrium attainable. Just where that level is fixed will depend on how much, if any, urea is derived from the same katabolic processes that produce the creatinin. With reference to the remainder of the proteid involved, an extensive formation of Voit's "circulating proteid" followed by a second decomposition and elimination as urea seems almost, if not quite, as improbable as the corresponding formation and decomposition of Pflüger's organized protoplasm. Folin has therefore arrived at the following conclusion: The greater part of the protein furnished with standard diets represents exogenous metabolism and is not needed; or, to be more specific, its nitrogen is not needed. The organism has developed special facilities for getting rid of such excess of nitrogen so as to gain the use of the carbon moiety of the protein containing it. The first step in this process is the decomposition of proteid in the digestive tract into proteoses, amino-acids, ammonia, etc. The hydrolytic cleavages are carried further in the mucous membrane of the intestines, and are completed in the liver, each decomposition being such as to further the formation of urea.

We have in these special hydrolytic decompositions, the result of which is to remove the unnecessary nitrogen, an explanation of why and how the animal organism tends to maintain nitrogen equilibrium even when excessive amounts of protein are furnished with the food. This excess is not stored up in the organism as such, because the actual need of nitrogen is so small that an excess is always furnished with the food. The ordinary food of the average man contains more nitrogen than the organism can use, and increasing the nitrogen still further will therefore necessarily only lead to an immediate increase in the elimination of urea, and does not increase the proteid katabolism involved in the creatinin formation any more than does an increased supply of fats and carbohydrates.

Finally, the normal human organism can be made at almost any time to store up fats and carbohydrates. The katabolism of these products consists chiefly of oxidation, a decomposition which sets free large quantities of energy useful to the organism. The hydrolytic removal of nitrogen from protein involves by comparison a very small transformation of energy and yields a non-nitrogenous rest of great fuel value. The latter may be directly transported in part to the different tissues, and thus at once supply oxidative material where needed, but in all probability it is partly converted into fats, or at least into carbohydrates, and then becomes subject to the laws governing the katabolism of these two groups of food products. It may be added, there is no urgent reason for assuming that the katabolism of the proteid nitrogenous derivatives is brought about by oxidations like those which decompose the fats and the carbohydrates; for such cleavages are more easily accomplished by hydrolytic reactions than by oxidations.

The experience of the writers lends support to many features of the theory of proteid metabolism outlined by Folin. It makes intelligible the ordinary absence of any demonstrable effect of physical work on nitrogen elimination, and indicates how excess of nitrogen furnished with the food is quickly converted under normal circumstances into urea and made harmless by elimination. Even in starvation it is presumably not the muscle proteid which is first attacked. Folin suggests the following explanation for this case: "All living protoplasm in the animal organism is suspended in a fluid very rich in protein, and on account of the habitual use of more nitrogenous food than the tissues can use as protein, the organism is ordinarily in possession of approximately the maximum amount of reserve protein in solution that it can advantageously retain. When the supply of food protein is stopped, the excess of reserve protein inside the organism is still sufficient to cause a rather large destruction of protein during the first day or two of protein starvation, and after that the protein katabolism is very small, provided sufficient non-nitrogenous food is available. But even then, and for many days thereafter, the protoplasm of the tissues has still an abundant supply of dissolved protein and the normal activity of such tissues as the muscles is not at all impaired or diminished. When 30 or 40 grams of nitrogen have been lost by an average-sized man during a week or more of abstinence from nitrogenous food, the living muscle tissues are still well supplied with all the protein that they can use. That this is so, is indicated on the one hand by the unchanged creatinin elimination, and on the other by the fact that one experiences no feeling of unusual fatigue or of inability to do one's customary work. Because the organism at the end of such an experiment still has an abundance of available protein in the nutritive fluids, it is at once seemingly wasteful of nitrogen when return is made to nitrogenous food. This is why it only gradually, and only under the prolonged pressure of an excessive supply of food protein, again acquires its original maximum store of this reserve material."

If views such as this approach the truth, it is obvious that the prevailing ideas regarding the high proteid requirement of man are erroneous. We shall refer to this when treating of the dietetic needs of the body, in connection with the determination of the minimum proteid requirement. Landergren has observed that nitrogen elimination may fall to a low level on a nitrogen-free diet, and that the extent of the endogenous output under these circumstances is conditioned by the presence of a certain amount of carbohydrate in the food. So long as the carbohydrate requirement can be satisfied, the output of nitrogen is minimal. In the absence of carbohydrate an additional quantity of proteid is destroyed, perhaps to furnish sugar for the blood, and this additional loss cannot be prevented by the feeding of fat. According to Landergren, a third or more of the proteid destruction in hunger is attributable to the demand of the organism for carbohydrate which is accordingly furnished from the carbon moiety of the proteids. In this way, the increased proteid destruction noted during complete inanition in contrast with specific nitrogen starvation is explained.

The Proteids in Intermediary Metabolism.—If we follow more closely the history of the various nitrogenous urinary constituents we shall find that they represent quite distinct processes in intermediary metabolism. The

urea output, in proportion to the total nitrogen elimination, may be greatly diminished in disease. The experiments of Folin make it probable that even in health the urea fraction of the nitrogenous excretives may be very greatly reduced when the minimum proteid requirement of the organism is not overstepped. The theories bearing on the immediate origin of urea are numerous and cannot be examined here in detail.

Urea.—It is well known that the liver has the power of forming urea from ammonium salts, and from simple amino-acids like glycocoll. The evidence is increasing to indicate a larger proportion of ammonia in the portal blood, especially at the height of digestion, than is found in the hepatic vein. Digestion thus furnishes many factors which may play a part in the synthesis of urea. Some of the tissues contain urea-forming enzymes. Thus *arginase* acts upon the proteolytic derivative arginin to form urea and ornithin and this mode of origin may explain the occurrence of urea when the liver is completely excluded. That the liver is the chief organ involved in urea formation is suggested by the results found when it is completely excluded from the circulation. A greatly increased elimination of ammonia follows, with diminution in the output of urea; the latter, however, never completely disappears, possibly owing to its production from proteolytic products like arginin in various parts of the body by the agency of urea-forming enzymes. Kossel has already found *arginase* in various tissues. There is no evidence of the direct formation of urea from proteids in the body, although Hofmeister has succeeded in forming it by oxidation with permanganate in the presence of ammonia at 40° C. from both nitrogenous and non-nitrogenous compounds.

In certain diseases, especially such as seriously involve the functions of the liver, the proportion of urea nitrogen eliminated may diminish very markedly, falling even below 10 per cent. of the total output. In some instances this may be due to the small intake of proteid and corresponding diminution of exogenous proteid metabolism. But as the output of ammonia is almost always very large in these cases, amounting at times to 40 per cent. of the entire nitrogen output, it is more likely that the formation of acid products in intermediary metabolism—the condition known as acidosis—may draw upon the ammonia for purposes of neutralization. For this reason, the elimination of ammonia is increased by administration of mineral acids; and under such conditions and in such diseases as in fevers and diabetes, where an increased formation of acid takes place, the quantity of ammonia in the urine is increased. The ammonia may be afforded by additional proteid katabolism and the destructive removal of fixed alkali thus prevented. The absolute quantity of ammonia eliminated ordinarily is small,—approximately one-half gram per day.

Creatinin.—The current views regarding the significance of creatinin in the urine have experienced a marked change in recent times. The traditional opinion is that creatinin in the urine is largely derived from the creatin of meat ingested. We have observed, however, that creatinin and creatin are not lacking in the urine of suckling animals, contrary to the statements of most writers. That the creatinin output is at once increased by ingestion of meat has received abundant confirmation. On the other hand, both Long and the authors have, in distinction from several other investigators, found creatinin abundant in the urine of vegetarians who

abstained for months from meat or other creatin-containing foods. Folin maintains that the absolute quantity of creatinin eliminated in the urine on a meat-free diet is a constant quantity different for different individuals, but wholly independent of quantitative changes in the total amount of nitrogen eliminated. Creatinin in the urine would, on this assumption, become a measure of the extent of endogenous proteid metabolism under appropriate conditions of diet. Whether creatinin production is increased with excessive muscular work is as yet rather uncertain, as is the immediate antecedent of the creatinin. Lecithin has been suggested by Koch as a possible precursor, though the evidence is far from convincing. The experience of the writers agrees in many ways with the essential requirements of Folin's views. We have noted a production of creatinin in starvation in man, and have observed an elimination of this compound proportional, broadly speaking, to the body weight or bulk of the active tissues on diets practically creatin-free. The following summary represents average figures drawn from protocols regarding endogenous creatinin obtained in our laboratory:

Subject.	Body weight.	Creatinin.	Creatinin per kilo.
	<i>Kilos.</i>	<i>Grams.</i>	<i>Milligrams.</i>
A.C.	22	0.37	17
P.	27½	0.44	16
E.H.R.	57	1.10	19
R.H.C.	57½	0.87	15
G.M.B.	61½	1.17	19
O.E.C.	62½	1.46*	23*
F.P.U.	65	1.21	19
L.B.M.	70	1.18	17
J.I.	90	1.87*	21*

*These figures represent creatinin plus creatin.

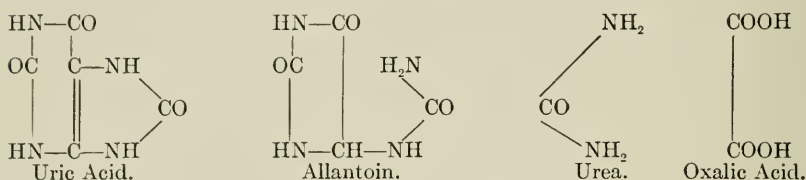
It is therefore not at all improbable that we may have in creatinin a most reliable index as to the extent of certain aspects of proteid metabolism—the tissue metabolism.

Purins.—In the case of uric acid and other purin derivatives, it is apparent from recent studies that there exists likewise a twofold source, *viz.*, an exogenous source related to the foodstuffs and an endogenous one. No convincing evidence has yet been furnished of a synthetic formation of uric acid in man, although this is a familiar process in birds and reptiles where uric acid represents the chief end-product of nitrogenous metabolism. The exogenous sources of uric acid production are found in all those compounds which contain the purin nucleus in a form in which it can be attacked in the body. They include especially the nucleoproteids (nucleins) occurring abundantly in glandular tissues like liver, thymus, kidney, etc. To this may be added the free purin bases like hypoxanthin and xanthin which are present in tissue extracts, especially in the muscle. In smaller quantity, nucleic acid derivatives and purin compounds are found in vegetable foods. In all these cases, the purin group is either present preformed or is liberated by metabolic (enzymatic) changes and

then oxidized further to uric acid, and in much smaller proportion appears in the form of other purin derivatives: xanthin, guanin, hypoxanthin, adenin, paraxanthin, heteroxanthin, etc. But even on a purin-free diet, or during starvation, uric acid continues to be eliminated in small, though noteworthy, amounts, and there is considerable evidence to show that this endogenous purin output is a fairly constant quantity for any individual, whatever the character of the (purin-free) diet. That the body is not entirely destitute of the power to form nucleoproteids, is seen in the construction of these compounds in the developing egg and in the growing infant nourished with milk, which is practically purin-free. In the purin metabolism of the adult, however, food purins are of foremost importance and the synthetic processes, if they occur at all, are inconspicuous.

In attempting to render account of the intermediary metabolism of the purins, it is apparent at once that we have to deal with a chemical transformation which, as in the case of creatinin, is quite independent of urea production and calls for a special interpretation. For many years it was believed that uric acid represented an intermediate stage in the katabolism of proteids to urea. It is indeed true that uric acid can readily be decomposed so as to yield urea and such a process doubtless occurs when uric acid is broken down in the body. Further than this the relation does not hold, since we have learned to recognize chemical differences in the nitrogenous foodstuffs, involving the presence of the purin group in some, and an entire absence of it in others. As an illustration of this, we may cite experiments of our own, in which 20 grams of nitrogen ingested largely in the form of sweetbread (thymus glands rich in nucleoproteid) afforded an output of nearly 2.0 grams of uric acid, whereas the same quantity of nitrogen taken in the form of the purin-free substances yielded only 0.3 gram of uric acid per day. The quantity of uric acid (and other purins) eliminated is not equivalent to the amount ingested, but represents only a fraction of it. Simultaneously with the tissue processes which result in the oxidative formation of uric acid, a destruction of the latter occurs; so that the quantity of uric acid actually excreted represents the equilibrium reached between the formation and further oxidation of that compound. Recent studies make it probable that tissue enzymes coöperate in these changes in various ways. Nucleases may liberate the amino-purins, adenin, and guanin, from nucleoproteids or nucleic acids; amidases (adenase and guanase) transform these amino-purins to hypoxanthin and xanthin respectively; and oxidases effect an oxidation of the latter to uric acid and even further. All of these reactions have been demonstrated with various tissue extracts; and it is interesting to observe that whereas many tissues, like the liver, testes, etc., which are rich in nucleoproteids, yield adenin and guanin on direct hydrolysis with acids, after autolysis they afford hypoxanthin and xanthin in place of the amino-purins. In addition to this, liver extracts are capable of oxidizing added xanthin and hypoxanthin to uric acid through intermediation of a special enzyme (xanthinoxidase), and to decompose the uric acid still further. A special influence on purin metabolism was at one time attributed to the spleen. Experiments by the writers have failed to substantiate such a view. In fact, there is no evidence that the spleen exerts any special influence on either

carbohydrate or proteid metabolism in general. The liver doubtless plays an important role in these reactions, especially in the destruction of the intermediary uric acid. Herein probably lies the explanation of the increased (or at least undiminished) output of uric acid in organic disturbances of the liver, involving a complete or partial exclusion of its functions. Thus, too, we may believe that substances which disturb these functions, as alcohol, facilitate increased uric acid output by diminishing the normal katabolic action. At any rate, the organism has the capacity, invested no doubt in different tissues, of converting food purins into uric acid which may escape destruction and be excreted as such, or may be further oxidized. When the latter occurs, allantoin has been demonstrated as a characteristic product, rarely arising in man, however. It is not unlikely that oxalic acid represents a further intermediary stage. The relation between these compounds is shown below:



The purin bases which serve as antecedents of endogenous uric acid have been supposed to arise from the nucleoproteids of disintegrated cells, in particular the leukocytes. As a matter of fact, increased elimination of uric acid has been observed in conditions attended with pronounced leukocyte destruction, enormous quantities (5 grams and over) having been reported in cases of leukæmia. If we may trust the observations of Burian, however, the greater bulk of the *endogenous* purins is formed in the muscles, thus explaining in a way the relative constancy of the endogenous uric acid production in the same individual as well as the variations attributable to different personality, *i. e.*, mass of active tissue.

Amino-acids.—The hippuric acid $\text{C}_6\text{H}_5\text{CO}.\text{NH}.\text{CH}_2\text{COOH}$ in human urine originates in part at least from aromatic substances derived from the diet, especially fruits and vegetables. Benzoic acid is speedily effective in bringing about the synthesis; and a small part may be formed indirectly through putrefactive processes in the intestine. The place of synthesis appears to be in the kidneys as well as other tissues. The glycocoll required to conjugate with the aromatic radical is derived from proteids. In fasting animals repeatedly fed with benzoates, the amount of glycocoll eliminated through the urine as hippuric acid (benzoyl-glycocoll), compared with the total nitrogen metabolism, indicates that 4 grams of glycocoll may be derived from the metabolism of every 100 grams of body proteid. The glycocoll excretion runs parallel with the proteid destroyed. Feeding carbohydrates does not increase the formation of glycocoll; but the proportions formed after feeding gelatin and casein are between 3 and 4 per cent. of the proteid metabolized. The formation of glycocoll in the body is unquestioned; and the significance of the hippuric acid eliminated is therefore connected with the origin of the benzoic acid.

Of the sulphur compounds in the urine, the ethereal sulphates represent vehicles of elimination for different conjugated groups. In indican, the

organic radical is derived from indol formed by intestinal putrefaction from the tryptophan group in the proteids. In accordance with this view, Underhill has found that after feeding gelatin (which contains no tryptophan group) in place of ordinary proteids, the excretion of indican is greatly diminished. The ethereal sulphates also represent other organic radicals like phenyl and cresyl. The immediate source of all these components is not yet established. The inorganic sulphates appear to follow the fluctuations of urea, the neutral sulphur on the other hand showing a possible connection with some endogenous proteid katabolic process.

Pathology has furnished several illustrations of perverted metabolism of proteids, which throw some light on the character of the normal intermediary changes. In alkaptonuria, the usual destruction of the aromatic proteid cleavage products, tyrosin and phenylalanin, appears to be interfered with. Under conditions of health these compounds are completely burned in the body; but in the anomalous condition under consideration they leave the body as homogentisic or uroleucic acid.

That the "alkapton" substances owe their origin to the aromatic group of the proteid molecule is evident from the proportionate relation between homogentisic acid and proteid destruction, and the fact that the quantity of the acid eliminated after a diet of some specific proteid substance is generally equivalent to the amount of tyrosin and phenylalanin yielded by it. Furthermore, feeding of tyrosin and phenylalanin to patients with alkaptonuria is followed by increased output of homogentisic acid, whereas in normal individuals these aromatic amino-acids are completely burned up. The experimental evidence gives no support to the idea of an *abnormal* production of homogentisic acid from proteids in this disease; but rather that the katabolism of the aromatic complexes ordinarily proceeds through the stages above described, and in alkaptonuria meets with a condition where the final cleavage of the benzene ring represented in homogentisic acid is no longer possible. Accordingly, the healthy individual readily burns up ingested homogentisic acid, while in alkaptonuria it is excreted unchanged.

Cystinuria furnishes another pathological condition which consists in an inability to burn some of the amino-acids formed in intermediary metabolism, notably the sulphur-containing complex of the proteids represented by cystin. When this compound is fed to healthy individuals in quantities as large as 8 grams, it is completely oxidized and the sulphur is eliminated in the form of sulphates and thiosulphates. It may in part be converted into taurin and enter into the composition of the bile as taurocholic acid. The relation of proteids to the production of bile salts thus becomes clear in the case of glycocholic and taurocholic acids, since the origin of glycocholic and taurin in the intermediary metabolism of proteids is understood.

Normally, urine is free from cystin even when the latter is fed; but when cystin is given to cystinuric patients it may be in part excreted again. There is at present some divergence of opinion on this point. It is further claimed that cystin is not the only amino-acid which is not burned in cystinuria; in some cases it has been reported that ingested tyrosin and aspartic acid are excreted unchanged. The diamino-acids take a peculiar position in the metabolism of some of the cystinuric individuals. They are partly split up with liberation of carbon dioxide

and reappear as diamines. It is likely that this change is attributable to the action of intestinal bacteria, so that the diamines are absorbed as such from the intestine and eliminated unchanged. This seems the more probable because the diamines here concerned, putrescin and cadaverin, have been produced experimentally by the action of bacteria upon the diamino-acids, arginin and lysin, and the diamines are found in the faeces as well as the urine in cystinuria. Arginin is doubtless first converted into urea and ornithin, which in turn is transformed into putrescin and carbon dioxide. The interesting cases of cystinuria and diaminuria frequently found combined in the same individual, give further evidence of stages through which proteids presumably may pass in their normal katabolism, and at which the decompositions may be arrested in pathological conditions. Further evidence of the formation of cystin as a normal intermediary stage in proteid katabolism has been afforded by a type of experimental cystinuria made known by Baumann. Dogs fed with brombenzol excrete the so-called mercapturic acid, which readily yields bromphenyl cystein, the halogen benzol compound apparently protecting the cystin radical from oxidation. Doubtless there are varying degrees of incapacity for the katabolism of proteids in different patients, just as we have different degrees of inability to burn sugar in diabetics.

Additional evidence regarding the occurrence of the characteristic proteolytic derivatives as stages in intermediary metabolism is gradually accumulating. Aside from the typical conditions described above, there are other pathological states in which unoxidized amino-acids are excreted in complete analogy with the ideas we have put forward regarding elimination of the intermediary products of carbohydrate katabolism, exemplified in glycuronic acid and oxalic acid. Thus, in acute yellow atrophy of the liver, in phosphorus poisoning, in gout, pneumonia, and leukæmia, tyrosin, leucin, glycocoll, etc., have been isolated from the urine, from which they are absent in health even when introduced as such into the organism. The conditions met with in these cases may be classed as *perversions or disturbances in the metabolism of the amino-acids*.

We have seen that nucleoproteids follow transformations in metabolism somewhat distinct from those of the simpler proteids, the characteristic differences being associated with the purin complexes in particular. It is not unnatural, therefore, that perversions of *purin* metabolism should occur. The phenomena of gout have long been associated with such disturbances, and the discussion of the pathology of this condition has been prominently connected with the behavior of uric acid in the body, though with somewhat questionable justification at times. It would be unprofitable to review the enormous literature on this subject here; yet it is impossible to make any concise statements which are at all adequate or undebatable. Certain features connected with purin metabolism in gout deserve mention. The particular attention which has been directed to uric acid in this connection has arisen primarily from the fact that urate depositions unquestionably are found in the tissues and joints. The cause for this is quite uncertain. It is true that the blood in gout has been found to be richer than usual in dissolved uric acid; but it is by no means saturated with purin compounds, and from this point of view no apparent occasion for a deposition exists.

Certain it is that both in experimental gout (produced by meat feeding to animals) and in human gout the liver is frequently involved. The important influence of this organ has been noted especially by the writers in studying the fate of uric acid injected intravenously. In animals, allantoin is produced in this way; the quantity is far greater, however, after injection directly into the portal circulation than into a systemic vein.

Acute attacks of gout are accompanied by marked variations in the elimination of uric acid, a retention or deposition of the latter being followed by a sweeping out, as it were, of accumulated urates. In many cases, the *rate* of uric acid elimination after a meal containing meat is greatly altered in comparison with the healthy individual. Questions of solubility may be concerned herein. Enough has been said, we think, to indicate that in gout it is not so much a disturbance in purin metabolism as a perverted function of one or more organs and tissues which is of pathogenetic moment.

Before leaving the subject of proteid metabolism, we must consider one aspect of the *anabolism* of proteid which frequently attains clinical importance. Can the organism build or store up proteid elements in the form of flesh (*Fleischmast*), in distinction from fattening. As a continuous process this is impossible in view of the tendency toward nitrogen equilibrium which has already been explained. Otherwise the growth of muscle, for example, might be facilitated enormously. As a matter of fact, flesh formation, whether directly from circulating proteid, or indirectly from proteid cleavage fragments, can at times be accomplished. It seems to depend primarily upon the nutritive condition of the cells rather than upon any surplus of food. Proteid tissue anabolism may take place in the muscles as it is seen in hypertrophy induced by vigorous muscular work; it is characteristic of growth in the developing organism; and can also be induced in the adult organism after malnutrition or undernourishment. In all of these instances, nitrogen retention may accompany the regeneration of the protoplasm.

Pathology of Nutrition.—In outlining the more important features in the metabolism of proteids, fats, and carbohydrates, numerous references have been made to pathological variations in the transformations which these compounds undergo. Thus, the bearing of gout and diabetes upon the metabolism of purins and carbohydrates has been pointed out; and some of the features of the abnormal katabolism of the proteids illustrated in the case of alkaptonuria, cystinuria, and diaminuria. In this section we propose to consider certain more general and unrelated phenomena which are of interest in the study of the pathology of nutrition.

Autolysis and Intracellular Enzymes.—The recognition of the importance of enzymatic processes, and the increasing acquaintance with types of enzymes capable of transacting the work of the cells under physiological conditions, has directed attention to the possible significance of these enzymes in pathological processes. As certain functional activities have long been associated with definite morphological structures, the integrity of which was conceived to be essential for their work, pathology has depended upon structural or vague "functional" alterations to account for the unusual or abnormal. But since proteolysis, lipolysis, glycolysis, oxidation, deamidization, are all referable to appro-

priate enzymes, some of which seem to be regulated by corresponding anti-enzymes or activated by kinases, new features are introduced into the study of pathological manifestations. In a system of coöperating and interdependent chemical reactions, it is quite conceivable that the impairment or omission of one link in the chain may throw the entire complex out of gear. The autolysis of certain tissues in disease is doubtless associated with some such disturbance. Autolytic enzymes are widely distributed; and in phosphorus poisoning and acute yellow atrophy an intravital autolysis of the liver frequently leads to a softening of that organ, with formation of typical products of proteolysis. In carcinoma, in the lungs during pneumonia, in abscess formation, and especially where a destruction of polynuclear leukocytes is accompanied by a liberation of autolytic enzymes, autolytic changes may take place. The proteolytic products are then further destroyed in the usual ways, or they may accumulate in the blood and be excreted as such. Autolysis seems to be the effective agent in the destruction or metabolism of all necrotic tissues. The occurrence of amino-acids, like leucin, tyrosin, and glycocoll in the urine, is perhaps attributable in some cases to undue autolysis which is checked in conditions of health. It is not unlikely that analogous changes take place in the degeneration of nervous tissue, by which cholin is liberated from lecithins. As further peculiar products of tissue self-digestion, bactericidal and antitoxic products may be mentioned; and lately the lack of suitable glycolytic enzymes has been proclaimed as a possible cause of the imperfect utilization of sugars in diabetes.

Acidosis.—This term is used to designate a pathological condition clearly pictured by Naunyn, in which acids arise in metabolism. It is not easy to determine in every case whether the acid owes its origin to abnormal formation, or to imperfect destruction of some compound ordinarily generated in intermediary metabolism and at once subjected to further decomposition. There are several ways in which these acid products may become a source of harm. They are likely to withdraw from the body bases in combination with which they are then eliminated as relatively harmless salts; and when the organism is overwhelmed with large quantities of these unneutralized organic acids, toxic symptoms may be occasioned. The most interesting feature of the general condition of acidosis, whatever the mode of its generation, is the accompanying increased elimination of ammonia. This, however, does not necessarily signify any increased production of ammonia in metabolism. Ammonia is the acid indicator of intermediary metabolism. When mineral acids are introduced into the body, or organic acids are formed by some unusual circumstance within it, they are at once neutralized by ammonia, the nitrogen elimination in other types of compounds being correspondingly diminished. The dangers of acid intoxication are thereby avoided, and the alkali content of the blood and tissues protected from loss. This typical behavior of ammonia in intermediary nitrogen exchange is a valuable protective reaction for the organism; and, conversely, the elimination of proportionately large quantities of nitrogen, in the form of ammonium salts, is to be referred not to any increased katabolism resulting in ammonia production, but rather to acids which have neutralized it prior to its conversion into urea. Of

possible conditions which might initiate such an excretion there are many. The intermediary production of lactic acid, β -oxybutyric acid, aceto-acetic acid, glycuronic acid, oxalic acid, etc., suggests the types of acid compounds which may be formed. It has already been suggested that a probable—perhaps the most plausible—theory of the origin of these compounds is one which refers them to arrested stages in normal katabolism. Hence they are wanting in the healthy organism. Mineral acids (phosphoric and sulphuric) may likewise arise in metabolism. As a rule, however, the quantity of these is far too small to account for the high ammonia output in many pathological conditions, and it is necessary to assume the production of a considerable portion of *organic acids*. There are even cases in which the production of acids is sufficiently large apparently to call forth a destruction of proteid in order to furnish sufficient ammonia for the acidosis presented.

When the quantities of the chief bases, sodium, potassium, calcium, magnesium, and ammonium, and the chief acids, sulphuric, phosphoric, hydrochloric, and uric, eliminated in the urine, are compared or “balanced,” any excess of the sum of the bases over the equivalent sum of the acids may at once be referred to the presence of unknown organic acids. In diabetes, where the carbohydrates are no longer burned up, the nutritive demands of the body draw upon the fat supply in correspondence with which the fat-content of the blood has actually been observed to be higher than usual. We have seen that β -oxybutyric acid and its derivatives, aceto-acetic acid and acetone, may arise in the katabolism of the fats. The diabetic patient in the advanced stages of the disease also loses his capacity to burn up β -oxybutyric acid in contrast with the normal individual in whom it is readily and completely oxidized. In the more extreme cases, other bases, calcium, magnesium, even potassium and sodium, may contribute to the “disintoxicating” or neutralizing process, and the body may be robbed of its bases in addition to losses of proteid katabolized to yield ammonia. The lethal symptoms in diabetic coma are those of an acid intoxication, while loss of alkali doubtless plays a contributory role in the effects produced. A severe acid intoxication tends to diminish the alkalinity of the blood markedly, and the carbon-dioxide content has been found to be diminished to one-sixth or less. Furthermore, the physiological capacity for excretion by the kidneys is not infrequently seriously impaired, so that imperfect elimination adds to the gravity of the situation.

The complications of perverted intermediary metabolism are far-reaching. The situation in diabetes is, perhaps, somewhat extreme, yet sufficiently characteristic to portray the salient features of acidosis. It is well, perhaps, to emphasize the fact that the fundamental disturbance is a nutritive one. Organic acids left unburned deplete the store of available bases. They may unite with ammonia, which the organism can almost always furnish with liberality when the proteid of the diet is present in customary abundance, or which it can requisition by increased katabolism if need be. Or the acids may unite with other bases and induce a new series of nutritive difficulties; so that there are cases in which the extent of ammonia output is not a reliable measure of the degree of acidosis. In such instances the “balance” of acids and bases must be depended on for more reliable indications.

All grades of acid intoxication may be observed. Thus Herter believes that small quantities of organic acids pass from the blood into the urine in cases of dilatation of the stomach and in some other disorders of digestion. The character of the pathological acid or acids has not been made out here with certainty. The evidence rests upon the observed excess of known bases over known acids in the urine. It is more likely that any organic acid formed in such gastric disturbance owes its origin to fermentative processes, than to some obscure metabolic disturbance caused by toxic products absorbed from the gastrointestinal tract.

There are various forms of hepatic disease accompanied and even characterized by the chemical symptoms of acidosis. Cirrhosis, degeneration following phosphorus poisoning, acute yellow atrophy, and chronic abnormality of the liver, differing in their pathogenesis, are all characterized by relatively high proportions of ammonia-nitrogen in the urine. The characteristic high ammonia elimination in liver affections may be associated with an inhibition of the urea-forming powers of the hepatic cells. Seldom is urea absent from the urine, however; and the low urea output may equally well be attributed, in the experience of the writers, to the small proteid intake of patients suffering from serious hepatic impairment. Furthermore, it has been found that even in advanced stages of hepatic degeneration ammonia salts administered by mouth can still be converted to urea. The differences which the metabolic disturbances may exhibit under changed conditions are well illustrated by the distinction between the phenomena of complete liver elimination in animals and those observed after production of the Eck fistula. When the liver is *completely* excluded from the circulation, ammonia is eliminated in abundance and urea decreases, as is true in Eck fistula cases; but the reaction of the urine becomes markedly *acid*, and it cannot be made alkaline even by administration of large doses of soda, although the ammonia output is thereby diminished. The marked acidosis is presumably attributable to other acids than those characteristic of diabetic derangement.

In many cases of acidosis the factor appears to be lactic acid, to which we are inclined to add various amino-acids—leucin, tyrosin, alanin, glycocoll—lately isolated from the urine of patients with severe hepatic insufficiency. Much of the lactic acid doubtless is referable to carbohydrates; some of it may be derived indirectly from proteids. Perfusion of the glycogen-yielding livers of well-nourished animals with blood results in a production of lactic acid—a result not noted when glycogen-free livers from starving animals are used. But alanin, a proteid derivative, likewise appears to form lactic acid under similar conditions. The relation between these compounds is very close. Contrasting these facts with the presumable origin of the pathological organic acids of diabetic urine from fats, it appears likely that acidosis as a condition can be brought about through imperfect intermediary metabolism of all the types of foodstuffs—fats, carbohydrates, and proteids.

An interesting disturbance of metabolism closely related to the phenomena of typical acidosis has been disclosed in connection with imperfect fat absorption from the intestine. When this is brought about by lack of bile secretion or pancreatic disease, the fatty acids liberated in

the alimentary tract from ingested fats appear to be excreted in the fæces in increased quantity as soaps of calcium and magnesium. The diversion of these alkali earths into this channel of elimination occasions diminished excretion of them in the urine. Indirectly, the formation of lime soaps leads to a deficiency of alkali and a compensatory elimination of ammonia—phenomena characteristic of acidosis in metabolism. It has been suggested that the high ammonia output of infants suffering from gastro-intestinal disturbances may be directly attributable to disturbed absorption of fat with the chain of consequences just outlined.

Obesity.—The physiology of fat formation and deposition in the body has already been considered. It is indeed difficult to say to what extent, if at all, corpulence represents a pathological condition; at any rate from a metabolic point of view the body is concerned here simply with an exaggeration of normal processes. When once a beginning has been made, the conditions thereby developed tend to perpetuate and aggravate the difficulties encountered. Thus with increase in weight and growing corpulence the body becomes less and less capable of active exertion, which in itself is conducive to further storage of fat. As the corpulence increases the muscles tend to be brought less into use, and the lack of exercise in turn tends to weaken them and render them still more unfit for work. The conservation of body warmth by the highly developed panniculus, the low metabolism of energy called forth by the attendant slothfulness, in addition to the abundant food intake in the corpulent, all contribute to protect the body fat. A cumulative effect thus induced can only be counteracted by a restricted intake and increased exercise, the latter being difficult because of the discomfort which it occasions. Alcohol plays a contributory part by affording a readily combustible compound which may speedily experience oxidation and protect the body-fat; and further, its pharmacological action is such as to contribute to the general indifference and inactivity characteristic of obesity.

These factors will be seen to be strictly within the province of normal physiological behavior. It has often been asked whether other elements do not contribute to the development of obesity. A hereditary tendency cannot be denied. The common observation of absence of any tendency toward corpulence in many individuals who eat very heartily and cultivate no unusual degree of muscular exertion leads one to ask whether the obese transform the potential energy of their foods more advantageously, or are subject to functionally diminished oxidative powers. Experiments have demonstrated conclusively that this is not the case. The oxygen consumption and carbon dioxide production of corpulent subjects is precisely comparable with that of non-corpulent individuals of the same weight. Even the supposedly "constitutional" obesity which is seen in castrated animals is referable to the lesser bodily activity. Finally, an influence on the part of the nervous system cannot be denied. As Müller expresses it, a vigorous individual whose spirit enters into continuous excitement and activity is certain to set his muscles into action to a far greater extent than the phlegmatic person who moves only when compelled.

Malnutrition and Related Conditions.—Ordinarily the disturbances noted are referable to variations in the quantitative relations of nutri-

tion. As soon as qualitative changes arise the term *malnutrition* is more appropriately applied to the distinctly morbid states, and here the phenomena of autolysis, acidosis, protoplasmic disintegration and retarded katabolism of specific molecular complexes are met with. As regards the relation of fever to metabolism, the etiological and clinical conditions are too diverse to permit any general theory. Fevers are usually accompanied by a noteworthy increase in proteid katabolism which contributes not a little to the serious physical impairment so often brought about. Undoubtedly it is quite correct to attribute this to a sort of involuntary inanition, but we believe that this alone is insufficient to account for all the disturbances of metabolism associated with fevers. Toxic products of bacterial or bodily origin undoubtedly may exert a direct action on tissue katabolism. In so-called "aseptic" fevers the glycogen-content of the body appears to determine in no small measure the possibility of the rise in temperature. That the processes of intermediary metabolism may suffer qualitative disturbances is suggested by experiments like those of Mandel on the purin bases in aseptic fevers. A pronounced coincidence between the temperature and the purin bases has been observed; the quantity of uric acid eliminated varies with the alloxuric bases; that is, the latter increase in amount as the quantity of uric acid diminishes, and *vice versa*. It is therefore not unlikely that a distinct relation between the fever and the appearance of certain products of incomplete cell oxidation, as shown by the excretion of purin bases, exists. The supposition that these bodies are directly concerned in the production of fevers is strengthened by the fact that the administration of xanthin and caffeine produces a decided rise in body temperature in otherwise healthy individuals. Without attributing to the purin bases the sole cause of the febrile temperature in the "aseptic" cases, it may be safe to assume that if other substances are concerned they are of similar origin and nature, *i. e.*, intermediary products of metabolism, the source of which is to be looked for in the circulating leukocytes and tissue cells. "We may assume that in a number of pathological conditions the ability of the cells of the organism to oxidize certain substances is directly interfered with. Probably this applies to the so-called aseptic fevers as, for instance, rise of temperature after severe operations, anaesthesia, convulsions, poisons, cachexias of various forms. In all these disturbances we may suppose that temporary or more permanent injuries to the cells inhibit their oxidation ability for a shorter or longer period; the consequences will necessarily be less complete oxidation of substances to their proper end-products." (Mandel.)

A further specific factor is the continued new formation and simultaneous destruction of cells in inflamed areas. Where exudates are formed in considerable quantity an unusual addition may be made to the "circulating" proteid of the body; in such cases the body metabolizes the excess of proteid just as when an excess of the latter is furnished in the form of food. To what degree the disturbed thermogenic functions influence katabolism in fever is not determined beyond dispute. A retention of chlorides accompanying the increased proteid decomposition has been reported in many infectious diseases, like pneumonia and typhoid, which are attended with fever. It is not unlikely, however, that in most of these cases the deficient salt intake is the contributing cause. A marked acido-

sis, especially intense in infancy, frequently adds to the complications which metabolism experiences in fever.

Indicanuria can scarcely be spoken of as a disturbance of intermediary metabolism, inasmuch as the primary cause usually lies in the preliminary putrefactive decomposition which the foodstuffs undergo before leaving the alimentary tract. The products of putrefaction, indol, skatol, phenol, and cresol, are synthesized in the liver to ethereal sulphates or glycuronates. The question as to whether the indol derivative indican cannot also arise in intermediary metabolism—in cases which are characterized by vigorous tissue decomposition as in certain types of cachexia, in carcinoma of the stomach, etc.—has been actively discussed. We agree with Jaffé in concluding that the experimental evidence for a direct metabolic origin of indican is not convincing. At present no positive source of urinary indican is known outside of bacterial processes. The pathognomic significance of indicanuria (indoxyluria) is therefore restricted to the domain of those diseases which are attended with bacterial activity, either within or without the alimentary tract.

DIET AND DIETETICS.

The subject of *dietetics* has for its consideration the nutritive demands of the body in health and disease, and the conditions and means whereby they may satisfactorily be fulfilled. The problems are manifold; for the needs of an organism vary with the conditions to which it is subjected, and the response of the individual has been modified in no small degree by universal custom or personal tastes, as well as by his environment. The ideal diet for a healthy man is one which will maintain him in nutritive equilibrium. The physician, however, not infrequently has occasion to depart from the limits here proposed, when he aims to accomplish beneficial effects by overfeeding or by an insufficient diet.

The physiological demands of the body can be determined by direct experiment and expressed in somewhat general terms; as, for example, the total energy required to preserve the chemical integrity of the body and maintain its functions. The necessity for a *mixed* diet and the inadequacy of a diet composed exclusively of proteids have been explained. It need scarcely be repeated that chemical composition is, of itself, no safe criterion of the food value of any nutrient. The digestibility and consequent availability of the nutrients bear directly upon their dietetic value, and these factors are influenced in no small measure by physical conditions. Herein lies the significance of the natural texture of the food substances, their preparation by cooking and mechanical processes, the palatability of the product, and tolerance of the organism for it.

Up to the present time the statements regarding the dietetic needs of the body have been based very largely on the observed facts of consumption rather than upon actual trials. The statistical method has been applied, in order to learn the kinds and amounts of food materials consumed by persons in different localities, of different occupations, ages and sex, and under varying conditions. From such data dietary standards have been suggested, upon the general supposition that the body is best nourished when through long periods the food approximates the requirements thus

SUMMARIZED RESULTS OF DIETARY STUDIES IN THE UNITED STATES (QUANTITIES PER MAN PER DAY.)

	Number of studies included in averages.	ACTUALLY EATEN.			DIGESTIBLE.			Fuel Value.
		Protein.	Fat.	Carbohydrates.	Protein.	Fat.	Carbohydrates.	
		Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Calories.
PERSONS WITH ACTIVE WORK.								
Rowing clubs in New England.....	7	155	177	440	143	168	427	3955
Bicyclists in New York.....	3	186	186	651	171	177	631	5005
Football teams in Connecticut and California.....	2	226	354	634	208	336	615	6590
PERSONS WITH ORDINARY WORK.								
Farmers' families.....	10	97	130	467	89	124	453	3415
Mechanics' families.....	14	103	150	402	95	143	390	3355
Laborers' families in large cities.....	12	101	116	344	93	110	334	2810
Laborers' families in more comfortable circumstances.....	2	120	147	534	110	140	518	3925
PROFESSIONAL MEN.								
Lawyers, teachers, etc.....	14	104	125	423	96	119	410	3220
College clubs.....	15	107	148	459	98	141	445	3580
MEN WITH LITTLE OR NO EXERCISE.								
Men in respiration calorimeter.....	11	112	80	305	103	76	296	2380
PERSONS IN DESITUTE CIRCUMSTANCES.								
Poor families in New York City.....	11	93	95	407	86	90	395	2845
Laborers' families in Pittsburg, Pa.....	2	80	95	308	74	90	299	2400
MISCELLANEOUS.								
Negro families in Alabama.....	20	62	132	436	57	125	423	3165
Negro families in Virginia.....	19	109	159	444	100	151	342	3025
Italian families in Chicago.....	4	103	111	391	95	105	379	2965
French Canadians in Chicago.....	5	118	158	345	109	150	335	3200
Bohemian families in Chicago.....	8	115	101	360	106	96	349	2800
Inhabitants of Java Village, Columbian Exposition, 1893.....	1	66	19	254	61	18	246	1450
Russian Jews in Chicago.....	10	137	103	418	126	98	405	3135
Mexican families in New Mexico.....	4	94	71	613	86	67	395	3460
Chinese dentists in California.....	1	115	113	289	106	107	281	2620
Chinese laundrymen in California.....	1	135	76	566	124	72	349	3380
Chinese farm laborers in California.....	1	144	95	640	132	90	621	3985
Fruitarians.....	6	50	102	237	43	92	225	2655
Maine lumbermen.....	182	337	812	6995

established. In the compilation of much of this valuable statistical material the United States Department of Agriculture has rendered an important service. An illustration of the results reached by this method is given in the table on page 722 (Langworthy and Milner).

Data such as the foregoing compilations afford, merely disclose the dietetic *habits* of these individuals. It is unfortunate that more facts derived from actual studies of metabolism are not yet available, so that wide-reaching application cannot be made, based upon *physiological* conditions; for it has become somewhat questionable whether the current statistical standards represent the true needs of the organism. Custom and convenience have entered so largely into our modes of living and dictated so much in our alimentary habits, that we may be in danger of accepting their dictum as a physiological law without that critical revision which scientific consistency demands. A further error lies in the customary failure to pay sufficient regard to the variations in the size of different individuals and the consequent variations in the extent of metabolism occasioned thereby. Making allowances for variations in body weight, Rubner has calculated the nutritive requirements of persons of different sizes and the relative participation of the various foodstuffs as follows:

Body weight.		Energy metabolized.	Proteids.	Fats.	Carbohydrates.
Kilograms.		Calories (large).	Grams.	Grams.	Grams.
Light work	80	2864	134	49	356
	70	2631	123	46	327
	60	2368	111	41	294
	50	2102	90	37	262
	40	1810	84	32	225
Moderate work	80	3372	128	61	556
	70	3094	118	56	500
	60	2792	106	50	461
	50	2472	96	44	409
	40	2129	81	38	344

The peculiar role of proteids has lent a special interest and importance to the determination of the daily requirement of this group of foodstuffs. We have already seen that proteids are not drawn upon under ordinary conditions as sources of energy when muscular work is done, and that they differ from the other nutrients in showing no tendency toward storage in the body beyond certain very narrow limits. In recent years considerable attention has been devoted to the determination of the minimum proteid requirement of the organism. It seems self-evident regarding the albuminous foods in particular, that the smallest amount which will serve to keep the body in a state of high efficiency is physiologically the most economical, and hence the best adapted for its needs. In the dietary standards which have been proposed the well-known figures of Voit have experienced only slight revision. For the proteid elements in particular the requirements adopted by Voit have rarely been regarded as excessive. In the table on page 724 are the figures representing dietary standards advocated or determined by different investigators.

The figures given for the most part represent opinions formed from the data gained by direct analysis of the diets used. Can these

figures be taken to represent the minimal proteid requirement for the healthy man? If not, how far can the proteid intake be safely and advantageously diminished below the commonly accepted standards?

Investigator.	Proteids.	Carbohydrates.	Fats.	Fuel value.
	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Calories (large).</i>
Voit.....	118	500	56	3000
Moleschott.....	130	550	40	3160
Ranke.....	100	240	100	2324
Forster (Munich workmen) . .	132	457	81	3174
Hultgren and Landergren (Swedish workmen)	134	523	79	3436
Studmund.....	114	551	54	3229
Schmidt.....	105	541	63	3235
de Giaxa (Venetian peasants)	118	620	64	3623
Erisman (Russian workmen)	132	584	80	3675
Atwater (moderate muscular work).....	125	*	*	3400
Atwater (very hard muscular work).....	175	*	*	5500
Rubner (Turkish peasants)...	156	761	109	4776
Gautier (without work).....	78	488	50	2800
Gautier (hard work).....	167	692	71	4200

*With fat and carbohydrate sufficient to furnish the total energy indicated.

Obviously any attempt to determine the minimal proteid requirement on the basis of the nitrogen output in starvation may lead to error. For the energy requirements of the body must be met at any expense; and in the absence of other supply, tissue proteid may be destroyed far beyond the actual katabolism necessary when other suitable nutrients are furnished. The blood sugar for example must be maintained under all circumstances. Landergren has studied the extent of proteid katabolism in proteid starvation with and without an abundant diet of fat or carbohydrate. His experiments indicate that a healthy man receiving an abundance of non-nitrogenous nutrients, but practically no proteids, katabolizes proteid represented by no more than 3 to 4 grams of nitrogen per day. In combined proteid and carbohydrate starvation, the katabolism of body proteid may exceed that just noted by 100 per cent., despite a large intake of energy in the form of fat. From this it would appear that a certain minimum of carbohydrate, as well as proteid, is necessary for the maintenance of the sugar-content of the blood. As soon as stored carbohydrate (glycogen) is no longer available, sufficient proteid is destroyed to furnish the desired materials, the nitrogenous moiety being simultaneously eliminated as useless. If this is true, then there is a limit to the extent to which fats can replace carbohydrates in isodynamic amounts; and with this, experience corresponds. But with a certain as yet undefined minimum of carbohydrate given, fat and carbohydrates can replace each other in proteid-sparing effects; whereas in the absence of all carbohydrate, fats are proteid sparing in lesser degree. In starvation, according to Landergren, a third or more of the proteid decomposition is occasioned by the body's demand for carbohydrate—which the proteids alone can satisfy in this case.

From what has just been stated it follows that the minimum proteid requirement of man can only be determined correctly when due regard is had for the appropriate supply of non-nitrogenous as well as proteid nutri-

ents; and the condition of hunger fails to afford this opportunity. Trials have been made to attain nitrogen (proteid) equilibrium with diminished proteid intake. Not a few experiments have been unsatisfactory because the total nutritive demands of the body were not satisfied by exhibition of adequate quantities of fats and carbohydrates. It requires no argument to show that impairment of the body must sooner or later follow any continued insufficiency in the total supply of energy in the form of food. Nevertheless, not a few experiments on record have indicated the possibility of maintaining both nitrogenous and bodily equilibrium on an intake of proteid considerably smaller than that recognized in the so-called dietary standards. Usually this has been accomplished only when a fairly *large* amount of non-nitrogenous food was consumed. Kumagawa, weighing 48 kilos, maintained nitrogen equilibrium for some days on an intake including only 55 grams of proteid and a total fuel value of 2,480 large calories. The daily average nitrogen elimination through the urine was 6 grams, through the faeces 2 grams. The diet was purely vegetable. Breisacher, in experiments on himself extending over thirty days, found that an estimated intake of 2,600 calories in the daily diet sufficed to maintain him in nutritive equilibrium with an average daily nitrogen excretion of about 8 grams. Peschel obtained a satisfactory nitrogen balance for a brief period with 7 grams of nitrogen daily in the food, 5.3 grams appearing in the urine and 1.6 grams in the faeces. Likewise, Caspari and Glaessner in a five-days' experiment with two vegetarians noted no loss of nitrogen on intakes of 5.3 and 7.8 grams of nitrogen, and 2,700 and 4,560 calories respectively. More important are the experiments which Sivén conducted on himself. With a body weight of 60 kilos, he was able, in trials extending through a month, to establish nitrogenous equilibrium on 6.26 grams of nitrogen with comparatively low total intake of food, amounting to about 2,500 calories.

Such data as these surely warrant the question, How far are we justified in assuming the necessity for the rich proteid diet called for by the Voit standard and those like it? It is repeatedly stated that an abundance of food is a necessity for the maintenance of physical vigor and muscular activity. This view is certainly reinforced by the customs and habits of mankind; but we may well query whether our dietetic habits will bear criticism, and in the light of modern scientific inquiry we may even express doubt as to whether a rich proteid diet adds anything to our muscular energy or bodily strength.

The experiments hitherto reported have been continued only for brief periods; and recalling the marked resistance of the healthy body it would be amiss to draw any far-reaching conclusions from observations of this character. Further, attention must be given to the unfavorable effects which have been attributed to a low proteid diet fed to dogs for some time. Thus, Munk and Rosenheim both noted after six to eight weeks a loss of the power of absorption from the alimentary tract, loss of body weight, strength, and vigor, followed by death. Jägerroos likewise observed that there was after some months a striking disturbance of the intestines on a low proteid intake, which was, however, eventually traced to a distinct infection and probably not connected with the diminished quantity of proteid in the diet. One is impressed, in the study of these animal experiments, with the abnormal if not unhygienic conditions under which the

dogs were kept. The great monotony in the diet and restricted quarters to which they were subjected makes it highly questionable whether the diet of the animals was responsible for their poor health in the sense in which it has usually been interpreted. In prolonged experiments over seven hundred days on man, Neumann has found 70 to 80 grams of proteid per day to suffice for the maintenance ration, even with moderate additional food intake of 90 grams of fat and 300 grams of carbohydrate. He inclines to the belief that nitrogenous equilibrium can be maintained on various nutritive planes. Vegetarians have lived for years on a diet relatively poor in proteids without observing any disagreeable effects. Jaffa's observations on the fruitarians and nutarians of California "showed in every case that though the diet had a low protein and energy value, the subjects were apparently in excellent health and had been so during the five to eight years they had been living in this manner." In comparing the income and outgo of nitrogen on a diet composed mainly of nuts and fruits, it was observed in 2 subjects that 8 grams of nitrogen were sufficient to bring about nitrogen equilibrium, while with 2 other subjects the nitrogen required daily for equilibrium was about 10 grams. In harmony with Sivén, Jaffa believes that after the body has suffered a loss of nitrogen there is at once an effort to attain nitrogenous equilibrium, and that any gain of nitrogenous body material is a comparatively slow progress. If this is true, it is obvious that the living substance of the tissue protoplasm must be *slowly* formed from the proteid of the diet. This, says Jaffa, should serve as a warning to anyone contemplating any appreciable decrease in the proteid of the daily diet.

A further statement made by Jaffa serves to illustrate the attitude taken by many physiologists on this question. "Even if it could be proved," he writes, "by a large number of experiments that nitrogen equilibrium can be maintained on a small amount of protein, it would still be a great question whether or not it would be wise to do so. There must certainly be a constant effort on the part of the human organism to attain this condition, and with a low protein supply it might be forced to do so under conditions of strain. In such a case the bad results might be slow in manifesting themselves, but might also be serious and lasting. It has also been suggested that when living at a fairly high protein level the body is more resistant to disease and other strains than when the protein level is low." While these suggestions merit careful consideration, it is equally evident that there is another side to the question. The elimination of the excess of nitrogen may become physiologically burdensome and uneconomical, if not positively harmful. Hence, we may well query on which side lies the greater danger without magnifying it on the one hand or suppressing efforts directed toward the true proteid minimum on the other.

With the purpose of throwing light upon the question of the proteid minimum and ascertaining how far, if at all, the intake of proteid food can be diminished without deleterious effects, an extensive series of experiments on man has been conducted in the laboratory of the writers. Recognizing that the maintenance of nitrogen and body equilibrium on a lower proteid standard than that generally adopted would have little practical value and would not escape justifiable criticism unless the period of trial was extended over a long time, arrangements were made

to realize this as far as possible. The experiments were conducted upon three distinct types of individuals: (1) Professional men who while leading active lives were not engaged in very active muscular work. They represent the mental rather than the physical worker. (2) A detail of men from the Hospital Corps of the United States Army, as representatives of the moderate worker. These men, of different ages and temperaments, took vigorous systematic exercise in addition to the routine work connected with their daily life as members of the hospital corps. (3) A group of university students who were thoroughly trained athletes, and some of them with exceptional records in athletic events. The records of these observations have already been published in Chittenden's *Physiological Economy in Nutrition* from which the data here presented are taken.

With reference to the general conduct of the experiments it should be emphasized that monotony of diet was avoided as far as possible, in due recognition of the psychical influences liable to affect secretion and digestion, and of the danger which continued exhibition of an unvaried diet may bring, in the lack or disproportion of certain inorganic elements in the course of a long period. The coöperation of a large number of subjects under different conditions of life and activity and with widely varying tastes must tend to exclude personal idiosyncrasies and thereby minimize the chance of misleading conclusions. The professional group exercised a free choice in the character and quantities of the foodstuffs consumed. For the soldiers a dietary was specially arranged, the character and quantity of food for each meal being prescribed with due regard to the satisfaction of their desires. Preliminary observations were made on these men with a dietary such as they were accustomed to, in the form of the ordinary army ration which has a high content of proteid. The diet was then modified *very gradually* by the introduction of various articles in place of meat, until finally for months the heavier proteid foods were greatly reduced in amount and replaced in a measure by carbohydrate foods. While vegetable foods eventually predominated, there was at no time a complete change to a vegetable or vegetarian diet. The student athletes likewise lived on a prescribed diet, with somewhat greater range of choice. There were no restrictions as to quantity of food in their case.

The method of observation consisted in a daily collection and measurement of urine and fæces. The nitrogen output in the urine was accurately determined throughout the experiment, extending from six to nine months or longer. At intervals the daily loss of nitrogen in the fæces was determined. Finally the balance between income and outgo of nitrogen was exactly ascertained several times for periods of about a week. The total intake of food in terms of heat units was approximately estimated without direct measurement. The statistics on this point are therefore of subordinate value. It may be noted that the body weight of some of the individuals gradually fell until a certain stationary "level" was reached, about which small daily fluctuations were observed. This was true of all who had any considerable accumulation of reserve fat. In the well-trained men of slender or athletic build these initiatory changes in weight were not so apparent, if they occurred at all. One of the writers (C), of 57 kilos body weight, showed an aver-

age daily nitrogen output of 5.7 grams in the urine for nearly nine consecutive months. Nitrogen equilibrium and body weight were maintained. The other writer (M), with a body weight of 70 kilos, established from an original weight of 76 kilos, likewise maintained health, strength and equilibrium with an average daily output of 6.5 grams of nitrogen in the urine. A third subject (U), of 65 kilos body weight, maintained health without increasing the total fuel value of the food, with an average daily output of about 7.5 grams of nitrogen for many months. These figures imply a daily proteid metabolism equivalent to about 0.1 gram of nitrogen per kilo of body weight, or half of that which custom and habit prescribe.

It should be said that these limits could only be reached with maintenance of nitrogen equilibrium, provided the total food supply was adequate. Our estimates indicate that the latter, far from being excessive, tended to fall below the ordinarily accepted standard of 3,000 large calories for a man of average body weight and moderate work. The adaptation to the new standards was gradual in each case.

The results obtained with the soldiers, living on a prescribed diet and exposed to the strain of military duties, together with gymnastic work and training, confirm the conclusions arrived at with the professional group from which some data are quoted above. Once accustomed to a more sparing proteid diet, less rich in nitrogen, these subjects had no difficulty in maintaining body weight on the food provided, and when the conditions were satisfactorily adjusted nitrogen equilibrium could readily be preserved. The members of the soldier detail were able to live for five consecutive months with a proteid metabolism corresponding to about 8 grams of nitrogen per day without discomfort or loss of vigor. The athletes, as well as the physically less active men, likewise met their ordinary requirements for several months on an average daily proteid intake of about 60 grams. Moreover, careful dynamometer and other tests, made at regular intervals on the soldiers and athletes, indicated an increase in muscular strength while the men were on the restricted diet. The summary on page 729 of a balance experiment lasting one week will illustrate the general character of the nitrogen results obtained in all of the experiments. The subject was a vigorous athlete of 63 kilos body weight.

It is interesting to compare the previous dietetic habits of some of our subjects in respect to the proteid intake. During two weeks, at the beginning of the experiment on the soldiers when the ordinary army ration was used, the daily output of urinary nitrogen not infrequently exceeded 20 grams and usually reached over 16 grams (equivalent to 100 to 125 grams of proteid). The subsequent record of these subjects is given on page 729.

We believe that these experiments demonstrate the possibilities of a physiological economy corresponding to a saving of considerable proteid food. Aside from its possible economic or sociological importance this may not be without physiological significance. The results are presented as a contribution to the solution of a serious problem. If the data obtained in these experiments, representing a proteid requirement 50 per cent. lower than the figures usually quoted as necessary to maintain strength and health, approach with any degree of accuracy to the true

NITROGEN BALANCE.

	Nitrogen taken in.	Nitrogen in urine.	Output.	Weight of faeces (dry).
	<i>Grams.</i>	<i>Grams.</i>		<i>Grams.</i>
May 18	8.119	5.75		...
May 19	9.482	6.64		15
May 20	10.560	8.45		...
May 21	8.992	8.64		...
May 22	9.025	8.53		...
May 23	8.393	7.69		89
May 24	7.284	7.34		24
				128—contain 6.40% N.
	61.855	53.04	+	8.192 grams nitrogen.
	61.855 grams nitrogen.			61.232 grams nitrogen.
	Nitrogen balance for seven days			= +0.623 gram.
	Nitrogen balance per day			= +0.089 gram.
	Average nitrogen intake per day			= 8.83 grams.

minimal requirement of the men under observation, we believe that the physiological needs of the body can be served for an indefinite period on a greatly lessened proteid metabolism. The fact that the greater part of the nitrogen contained in an ordinary diet, including 120 to 150 grams of proteid per day, is speedily eliminated lends favor to the view that it can satisfactorily be replaced by other foodstuffs. As Folin has said: "Nitrogen enough to provide liberally for the endogenous metabolism and for the maintenance of a sufficient supply of reserve protein

NAME.	Body weight. October, 1903.	Body weight. April, 1904.	Average daily urinary nitrogen. November–April.	Metabolized nitrogen, per kilo of body weight. ¹
	<i>Kilos.</i>	<i>Kilos.</i>	<i>Grams.</i>	<i>Gram.</i>
Fritz.....	76.0	72.6	7.84	0.106
Oakman...	66.7	62.1	7.42	0.116
Morris.....	59.2	59.0	7.03	0.119
Broyles...	59.4	61.0	7.26	0.120
Henderson	71.3	71.0	8.91	0.125
Loewenthal	60.1	59.0	7.38	0.125
Cohn.....	65.0	62.6	8.05	0.126
Steltz....	52.3	53.0	7.13	0.134
Slincy.....	61.3	60.6	8.39	0.138
Coffman...	59.1	58.0	8.17	0.140
Zooman...	54.0	55.0	8.25	0.150

¹ In this calculation the figures used for body weight are those of April, or where there is much difference the average of the October and April weights is used.

is shown to be necessary. But it ought neither to be necessary nor advantageous for the organism to split off and remove large quantities of nitrogen which it can neither use nor store up as reserve material."

In considering the possible physiological advantages of some reduction in the proteid element of the standard diet, it will be recalled that many of the disorders of metabolism involve the imperfect katabolism of proteid, so that nitrogenous derivatives other than urea are liable to arise. Lowered proteid intake, especially diminished meat consumption, means a decreased metabolism of the purins. This is illustrated in the observations made in our dietary studies from which the following table is taken:

AVERAGE DAILY EXCRETION THROUGH THE URINE FOR SEVEN TO NINE MONTHS.
PROFESSIONAL GROUP.

NAME.	Body weight.	Total nitrogen.	Uric acid.	Uric acid per kilo of body weight.	Phosphoric acid P_2O_5
	Kilos.	Grams.	Gram.	Gram.	Grams.
Chittenden....	57.0	5.69	0.392	0.0068	0.90
Mendel.....	70.0	6.53	0.419	0.0060	1.46
Underhill....	65.0	7.43	0.516	0.0079	1.28
Dean.....	65.0	8.99	0.386	0.0059	1.73
Beers.....	61.5	8.58	0.365	0.0059	1.49

The diet in these cases was very deficient in purin compounds as a rule. But even among the other groups where meat was more freely eaten, although in small amounts, the daily output of uric acid rarely exceeded 500 milligrams. It is difficult to see anything other than an advantage in a diminished production of intermediary products of proteid disintegration—for example, amino-acids and uric acid—under conditions where they are not properly converted into their appropriate end-products. This involves no assumption of any harmfulness of the excess of ordinary nitrogenous excretives in health. In disease, however, many conditions suggest themselves in which the clinician may do well to consider the therapeutic value of the possibilities involved in the foregoing discussion. This applies particularly to disorders in which the organs of proteid digestion (gastro-intestinal tract), metabolism (liver), and nitrogenous elimination (kidneys), are concerned. Furthermore, there is no lack of evidence that temporary *proteid* starvation is ordinarily not attended with any *immediate* deleterious effects, owing to a considerable proteid reserve in the body; so that the physician meeting with circumstances of disease complicated by the difficulties of the "mechanics" of nutrition, for example, may readily exchange the minimum temporary damage or loss occasioned by endogenous proteid katabolism in the absence of food, for permanent therapeutic gains.

If we pass to the data available regarding the total food demand of the body, expressed in terms of energy katabolized daily, statistics of actual food consumption show a fairly wide range between 1,500 and 4,000 large calories. These differences are conditioned in part by differences in the individuals studied, as well as by the variable demand created by unlike degrees of bodily activity. More exact information

may be expected from the increasing number of calorimetric observations made directly on man. In general the latter show a utilization of about 30 large calories per kilo of body weight during rest and fasting, increasing somewhat when food is administered, and rising to over twice this amount when muscular work is done. In cases of extreme exertion during many hours of the day, the transformation of energy may increase to 130 large calories per kilo of body weight. Calculated for a man of 70 kilos, the figures range from 2,100 to 9,000 large calories, the latter representing an extreme, yet not unreachd, figure. To what extent the more usual average metabolism of 3,000 calories per day represents the *actual* needs of the body of a 70 kilo man during moderate work cannot be conclusively determined at the present time. From such observations as we have been able to gather in our experiments of lowered proteid diet, we are inclined to the view that the customary standards for the total energy demands represent a high rather than a low limit; for such approximate valuations as we were able to give to the diets used in these experiments, and which are here mentioned with due reservation in view of the lack of direct fuel value determinations, indicated a metabolism of energy not greatly, if at all, exceeding 40 calories per kilo of body weight.

Among the better classes, the nutritive demands are certainly more than satisfied by the customary dietaries. Whether man can live on different nutritive planes, as various physiologists have suggested, remains to be seen. Any complete answer to such a question must, of course, take into consideration many factors more general in application than is indicated by bodily equilibrium alone. Mental as well as bodily efficiency, health and vigor must remain unimpaired. Much has been written about the relation of diet to the development and characteristics of races; a review of the literature soon convinces one, however, that it is impossible to form an unprejudiced judgment from the conflicting data, or unconfirmed opinions. Scientific observation has not yet replaced personal impressions to a sufficient degree in the study of this interesting question.

Muscular activity increases the demand for nutriment; but whether it increases the need for proteid seems very doubtful. The final answer will depend upon a determination of endogenous proteid metabolism during work, measurable perhaps by the output of creatinin. It is not unlikely that the wear and tear of the contractile tissues will be found somewhat increased by maintained activity. With a surplus of proteid in the diet, however, this does not make itself manifest in any study of total nitrogen exchange. As a rule we eat to satisfy the demands of the appetite without considering the true physiological needs of the body, or whether the appetite is in any degree proportioned to these. Perhaps the unwitting use of an excessive diet is occasioned by the modern culinary methods which make food palatable and attractive; and the danger in this direction applies more particularly to inactive, well-to-do persons than to the poorer working classes with a larger nutritive demand.

As to the relative participation of fats and carbohydrates in the satisfaction of the food requirements, it is well to recall the comparative food value of each. One hundred parts of fat are isodynamic with 230 parts of a carbohydrate, like starch. Each of these non-nitrogenous

nutrients is well utilized and the combinations are likewise rendered available in large degree. An excess of fat in the diet is liable to diminish the utilization of carbohydrate in the same ration. This doubtless explains the *apparent* failure of the widely advertised oatmeal diet in diabetes to cause sugar excretion. Very large quantities of fat (300 grams of butter or more) are prescribed with the oatmeal. The absorption of the latter is thereby doubtless greatly impaired and diminution of the glycosuria is attributable not to a better utilization of oat carbohydrates, but presumably to the imperfect absorption of the carbohydrate, which precludes its reappearance as diabetic sugar. On the other hand, an excess of carbohydrate in the intestine, especially in the form of coarse vegetable food, may become a severe burden to the alimentary tract. The extent to which fats and carbohydrates replace each other is, we believe, largely a matter of convenience, cost and individual taste. In general, fats are expensive and accordingly are allowed to furnish the smaller part of the energy. Zuntz and Schumburg have lately advocated a considerable increase in the fat foods of the German army ration, calling attention to the large food value of fats and their ready assimilation without much digestive work. They likewise suggest increased employment of sugar, the refreshing influence of which on the fatigued muscles has lately been announced. If it is remembered that one gram of fat is equivalent to 14 grams of milk, 9.8 grams of meat, 9.3 grams of potato, 30 to 40 grams of vegetables, it will be understood that fats may become a valuable adjuvant to the diet whenever a decrease in its bulk becomes desirable. Dietetic habits are frequently of moment in this connection. Individuals accustomed to concentrated diets may find a voluminous ration unattractive and even unendurable. In contrast with this, others find no satisfaction in any diet, however palatable or nutritive, unless it is sufficiently bulky. Only in this way can the feeling of hunger be dispelled.

To these creations of habit must be added certain idiosyncrasies which exhibit themselves in an intolerance for certain substances. In many cases these are immediately attributable to digestive disturbances or other recognizable disease. Not infrequently they are of a more subtle character. We see an illustration in the appearance of urticaria in otherwise healthy persons after eating shell-fish, strawberries, etc., indicating a susceptibility to minute quantities of chemical substances insufficient to affect the average individual in a perceptible manner.

Preparation of Food.—The preparation of food plays by no means a negligible part in its subsequent fate in nutrition and may contribute both to its digestibility and its palatability. The appearance, flavor, and odor, stimulate or modify the activity of the digestive glands through various channels, as has been shown so strikingly by Pawlow and his pupils. Food which is repulsive fails to provoke the proper digestive response, or at any rate calls it forth more slowly than an attractive meal does.

Man has been called a "cooking" animal, and the practice of subjecting foods to heat is well nigh universal. The rationale of the various ways of treating foods by means of heat is too little understood. In many cases it softens the foodstuffs and transforms their texture. The connective tissue fibers of meats are converted into gelatin by boiling,

so that they dissolve more readily and allow the digestive juices to act more directly upon the muscular fibers themselves. This change likewise facilitates the processes of mastication. Similarly, cooking changes the tough, firm make-up of many of the vegetables into soft and easily masticated tissue. In developing thereby a more pronounced flavor and odor, other factors of value are added. In vegetable foods the starch grains are ruptured and liberated in considerable proportion from the indigestible envelopes of cellulose which surround them. Further, the changes which starchy foods, like the cereals, undergo by dry heat are of value from the standpoint of lending flavor rather than because of any profound chemical changes effected. In the case of the legumes, peas, beans, etc., we have a good illustration of the importance of cooking for the proper utilization of such food materials. Finally, heat destroys many toxic substances or organisms present in uncooked foods and thus protects the body from dangers lurking therein.

A variety of substances classed as "food accessories" exert an influence quite independent of any direct nutritive value. Some, like the extractive substances of meat, etc., are not entirely devoid of fuel value; others, like some of the inorganic salts, are indispensable, despite the fact that they convey no energy to the organism; while another class still, including ordinary condiments such as pepper, mustard, and other spices, exert an indirect influence on nutrition. The latter class includes substances which act directly upon sense organs exciting the sense of taste and thus inducing a reflex flow of the digestive secretions. In so far as they stimulate the appetite, they may create favorable conditions for incipient alimentary changes by the indirect effect upon the secretory glands concerned therein. Pawlow has said: "Appetit ist Saft." The psychical effect of various factors in promoting, or—what is less familiarly recognized—in inhibiting indirectly the nutritive processes, is for the most part underestimated; for foodstuffs are not selected, in the ordinary course of events, with any due recognition of their real nutritive value, but rather in virtue of their palatability and the appeal which they make to the senses. Again, the group of substances represented by the extractives of meat as they are obtained in soups, etc., plays a part in stimulating the secretory glands. They are rapidly absorbed before the foodstuffs proper are digested, and in the blood-stream they act directly as secretory stimulants, inducing a flow of gastric juice. The question as to the effect of such substances upon the intermediate processes of metabolism has not yet received the consideration which it merits. Heretofore they have usually been studied from the standpoint of their pharmacological action. Yet taking alcohol as an illustration, the more distinctly physiological aspects seem worthy of attention. Observations in our laboratory have shown that it may noticeably alter the output of exogenous uric acid in man; and if other katabolic processes in the organism are similarly affected, the subsidiary changes induced in intermediary metabolism by such food accessories as alcohol may quite overshadow the influence which they exert in the preliminary digestive changes. It is impossible to say in what degree the demand for these accessories has been acquired by man; this much is evident, that in all culture lands the advance of civilization has been attended by increasing attention to the factors here discussed. Whether these subsidiary articles

of diet, including meat extractives, tea, coffee, chocolate, alcohol, etc., which are for the most part sources of little or no energy and not possessed of reparative power for the tissues of the body, are as necessary to us as the foodstuffs themselves is difficult to say. Common experience confirms their agreeable influence.

The inorganic salts, mineral nutrients or inorganic foodstuffs, are essential owing to the fact that a lack of them must inevitably lead to physiological difficulties as a result of their continued loss in the excretions. The conservative efforts of the body are frequently displayed in the marked retention of some of these elements; for example, of chlorine in fevers. But unless restitution is made the defect inevitably manifests itself sooner or later. From the quantitative point of view the demand for chlorine and sodium (sodium chloride) is most conspicuous, and the search for this salt appears to be almost instinctive in both man and animals. The pathological symptoms which lack of some of these elements, such as iron and calcium, develops, is familiar. Occasionally the difficulty presented apparently involves a deficient absorption or retention of the compounds. We are inclined to believe that an increasing familiarity with the distribution of inorganic salts and their elements in the natural foods will tend to lead to a substitution of *dietetic* methods of administration of these substances, in place of the therapeutic measures (artificial lime salts, iron salts, etc.) now employed so extensively. A radical change in diet will call for some consideration of the new adaptation of the inorganic foodstuffs accompanying it. Especially is this true for the growing organism. When the salts required by the latter are accurately known, a change from milk to some other form of diet may properly suggest the question whether the child will continue to obtain the necessary salts in sufficient quantities. Similar considerations apply to the convalescent period in invalids. The following table (from Bunge) indicates the range of variation in the constituents of the ash of the most important articles of diet, arranged according to the content of lime.

ONE HUNDRED PARTS OF DRIED SUBSTANCE CONTAIN.

	K ₂ O	Na ₂ O	CaO	MgO	Fe ₂ O ₃	P ₂ O ₅	Cl
Beef.....	1.66	0.32	0.029	0.152	0.020	1.83	0.28
Wheat.....	0.62	0.06	0.065	0.24	0.026	0.94	(?)
Potato.....	2.28	0.11	0.100	0.19	0.042	0.64	0.13
Egg-white.....	1.44	1.45	0.130	0.13	0.026	0.20	1.32
Peas.....	1.13	0.03	0.137	0.22	0.024	0.99	(?)
Human milk.....	0.58	0.17	0.243	0.05	0.003	0.35	0.32
Yolk of egg.....	0.27	0.17	0.380	0.06	0.040	1.90	0.35
Cow's milk.....	1.67	1.05	1.51	0.20	0.003	1.86	1.60

The marked differences in the distribution of important elements among these familiar dietetic articles is clearly shown. Thus, the poverty of cow's milk in iron and the relative abundance of lime are conspicuous. The total quantity of mineral ingredients included in the ordinary diet of the adult and their distribution has been compiled by Gautier, as shown in the table on page 735.

To the 17.43 grams of inorganic substances here accounted for, should be added 7 or 8 grams of common salt which are daily contributed directly to the food, making a total of 25 grams of inorganic compounds. It is

estimated that we excrete somewhat more than this quantity by the various channels of elimination. The slight gain is attributable to the sulphuric and phosphoric acids derived from the oxidation of organic compounds of sulphur and phosphorus ingested. It will also be noted

INORGANIC SALTS IN AN AVERAGE DAY'S RATION.

FOOD.	Total Weight.	Inorganic Salts.
	<i>Grams.</i>	<i>Grams.</i>
Bread and pastry.....	435	3.15
Meats.....	266	3.40
Milk.....	150	1.05
Eggs.....	30	0.03
Fresh fruits.....	90	0.45
Fresh vegetables.....	200	4.15
Dried vegetables.....	40	1.20
Potatoes.....	100	1.20
Cheese.....	12	0.80
Sugar.....	40	0.00
Butter.....	28	0.00
Wine.....	650	1.65
Drinking-water.....	1,000	0.35
		<hr/> 17.43

in the preceding table that the preponderance of the ingested inorganic compounds is associated with foods of vegetable origin; this applies in particular to specific elements: Potassium, magnesium and phosphates.

Composition of Foods in Their Relation to Nutrition.—Broadly speaking, it is customary to refer to the nutritive value of the various foods in daily use on the basis of their general composition; that is to say, the content of nitrogen or protein ($N \times 6.25$), fats (ether extract), non-nitrogenous constituents (digestible carbohydrates and insoluble cellulose), inorganic components and their heat of combustion. In discussing proteid metabolism it has already been pointed out that the nitrogenous compounds are by no means equivalent or identical in their physiological role, and the peculiar position of the purin-containing foods was emphasized. Up to the present time, relatively few data have been obtained with respect to the purin-content of foods in common use. The great divergence in the distribution of purin derivatives is made manifest in the figures compiled by Walker Hall, as shown in the table on page 736.

From this summary it is easy to arrange a dietary practically free from purin-containing foods and yet adapted to physiological requirements. For this diet cereals, milk, butter, eggs, certain green vegetables, sugars, etc., form the basis; and the output of urinary purins soon falls to the endogenous level thereon. In illustration of this we quote from Rockwood a diet experiment in which two subjects subsisted for nearly two weeks on a ration consisting of milk, 1,350 cc.; prepared cereal, 35 grams; sugar, 20 grams; crackers, 250 grams; cheese, 30 grams; eggs, 96 grams; apples, 90 grams; wheat bread, 50 grams; butter, 15

PURIN CONTENT OF COMMON FOODS.

FOOD.	Average percentage of purin nitrogen.	Purin bodies (grams per kilo).
FISH:		
Cod.....	0.023	0.582
Plaice.....	0.032	0.795
Halibut.....	0.041	1.020
Salmon.....	0.046	1.165
MEATS:		
Tripe.....	0.023	0.582
Mutton.....	0.038	0.965
Veal.....	0.046	1.162
Pork.....	0.048	1.212
Beef, ribs.....	0.045	1.137
Beefsteak.....	0.083	2.066
Liver.....	0.110	2.752
Sweetbread.....	0.402	10.063
Chicken.....	0.051	1.295
CEREALS:		
Bread, white.....	none
Rice.....	none
Oatmeal.....	0.021	0.530
VEGETABLES:		
Pea meal.....	0.015	0.390
Beans.....	0.025	0.637
Potatoes.....	trace	trace
Onions.....	0.003	0.090
Cabbage.....	none
Lettuce.....	none
Asparagus.....	0.009	0.215
BEERS.....	0.005	0.125
WINES.....	none
MILK.....	minute trace	minute trace

grams; confectionery, 100 grams; during this period the average daily outputs of nitrogen and uric acid in the urine were respectively:

	A.	B.
Nitrogen.....	11.580 grams	11.390 grams
Uric acid.....	0.305 grams	0.340 grams

The widespread and increasing use of cereal preparations of all sorts, which has come into vogue in recent years, may make it worth while to consider briefly to what extent some of the claims advanced have justification in truth. A comparison of animal foods with those of vegetable origin as sources of proteid and energy is afforded by the following figures (Milner):

	Proteid, per cent.	Energy per gram, calories (large).
Oat preparations.....	16.1	4.423
Wheat preparations.....	12.1	4.032
Corn preparations.....	8.6	3.894
Rice preparations.....	8.3	3.907
Beef, lean round.....	19.5	1.795
Beef, fat round.....	16.1	3.104
Bread, white.....	9.2	2.885
Bread, graham.....	8.9	2.872
Cheese, full cream.....	25.9	4.674
Potatoes.....	2.2	0.892

Milner has summarized the essential features with respect to modern cereal preparations, especially the ready-to-eat products, "breakfast foods," etc., in these words: "The difference between the various cereal preparations is principally one of process of manufacture. Some contain the whole of the grain, whereas with others the bran and germ have been removed in their preparation. Some are entirely uncooked, some are partially cooked, and some are wholly cooked and ready to eat as purchased. Among the latter are the so-called 'predigested' or 'malted' preparations.

"The composition of the different products depends upon that of the grain from which they are made, and the extent to which the bran and germ have been removed in the manufacture. In general, the prepared product from any grain has much the same composition as that of flour or meal from the same grain. Different brands of similar nature when made from the same grain do not differ in average composition any more widely than different lots of the same brand.

"Different prepared products from the same grain show no marked differences in respect to the amounts of nutrients that may be actually digested. The differences in actual nutritive value of the products from the same grain are therefore on the average so small that they may be disregarded in choosing between them. However, the oat preparations contain noticeably larger proportions of nutrients and energy than those of other grains, and as they are when properly cooked no less thoroughly digested the actual nutritive value of the oat preparations appears to be greater than that of the preparations from other grains.

"The nutritive value of the 'malted' or so-called 'predigested' preparations is no greater than that of other preparations from the same grains. In some instances the attempts to convert insoluble starch into more soluble material by the use of malt have been to a small degree successful, and to that extent the preparations have been rendered more easily digestible; but just as much and even more is accomplished by thorough cooking. In most of the malted preparations the quantity of starch actually converted is, however, very small and in some cases none has been changed.

"The thoroughness of cooking has quite as much influence upon the actual food value of the preparations as the small differences in composition. If the cereals are not thoroughly cooked some of the nutritive material will escape the action of the digestive juices."

Practical dietetics has long had to contend with a conflict of opinions regarding the true nutritive value of many familiar food materials. The errors are associated with exaggerated or incorrect ideas regarding the food value of specific dietary articles; and a prejudice against food materials of certain origin has been fostered in the absence of accurate scientific testimony. These statements apply to the medical profession as well as to the laity, who cannot always be expected to arrive at sound deductions on the problems of nutrition. Current notions regarding the relative value of different kinds of bread furnish an illustration of what has been said here. Wheat or rye flour is used most extensively, though some kinds of bread are prepared from barley or maize. The oat, on the other hand, will not yield a light porous bread. Further differences

are brought about by the choice of leavening agent used in preparing the dough.

In the manufacture of the commonly used "patent" wheat flour by the modern process of milling, the bran and aleurone layers, together with the germ, are removed by preliminary treatment and the remainder of the kernel is then ground. The bran, if included, would make the flour coarse; and the germ is removed because it contains oil, which acts upon the other constituents of the flour so that the bread in baking is darkened in color. The portions removed by the processes of refining are characterized especially by their richness in nitrogenous materials and inorganic salts. There has been much controversy regarding the nutritive value of the bran; and it has been claimed that valuable parts of the wheat are left in the waste cortical portions. To avoid this loss Graham flour is prepared by grinding the whole of the wheat kernel; and since no bolting or sorting process is introduced the product is in reality a wheat meal. As an intermediate product between the coarse Graham flour and the finest products, the so-called "whole wheat" or "entire wheat" flour has arisen. In this the attempt is made, with varying success, to remove only the woody part of the bran, leaving the aleurone layer and the germ with their nitrogenous and other ingredients and removing the irritating parts of the bran.

Experimental observations now recorded in large numbers indicate how unreliable chemical analysis alone may be in determining the relative nutritive value of the different grades of bread made from many kinds of flour. Actual trials on man show that wheat bread is more completely utilized than rye bread. Bread prepared from wheat flour is absorbed from the alimentary tract in larger or smaller amount according to the fineness of the flour used, the finest behaving most favorably in this respect. In cases where the flour is prepared from the whole grain there is always a considerably larger residue of unutilized food. The determining features are undoubtedly found in the varying physical peculiarities of the types of bread produced. That from fine wheat flour is far more porous than what is made from whole or crushed grains, and is thus more readily exposed to the digestive changes. Judging from the relatively large residuum of undigested material left after ingestion of the coarser kinds of bread, especially those containing considerable bran, the compounds included therein are protected from the digestive juices by their environment of cellulose and other indigestible substance and thus fail to contribute the food value which their composition alone discloses.

From digestion trials with breads Woods and Merrill conclude that "in general, the digestibility of the ration, whether simply bread and milk with a little butter and sugar, or a more varied diet, was decreased when the change was made from white bread to entire-wheat bread, and still further decreased when either was replaced by Graham bread, the remainder of the diet being, of course, the same in all three cases. The differences are sufficient to indicate that, even though the Graham flour contains the most and the white flour the least total protein of the three, the body would obtain more protein and energy from a pound of entire wheat than from a pound of Graham flour and still more from a pound of white flour than from either of the others. On

the other hand, it does not follow that a larger amount of digestible nutrients or available energy may not be obtained from 100 pounds of wheat when milled as Graham flour or entire-wheat flour than when ground into patent flour, because 100 pounds of cleaned and screened wheat will yield 100 pounds of Graham flour, about 85 pounds of entire-wheat flour, and only a little over 72 pounds of standard patent flour. This, however, is a question of pecuniary economy." They give as the amount of unabsorbable nitrogen for fine wheat bread, from 10 to 13 per cent.; for whole-wheat bread about 13 per cent.; and for Graham bread 23 to 24 per cent. of the food nitrogen.

On purely physiological grounds there is no justification for the extensive consumption of the coarser forms of bread among the masses of America and Europe. To many persons the taste of the coarse grades of bread is very agreeable. The bran is undoubtedly utilized to a small extent; but the justification for the therapeutic use of coarse breads is referable almost entirely to the more vigorous intestinal movements which they induce by virtue of a greater proportion of indigestible materials acting as irritants.

Experience accumulated in comparing the availability of proteids obtained from vegetable sources with those furnished by animal tissues has led to the inquiry whether these different types of proteids exhibit inherent differences in real digestibility. Not a few writers have assumed this to be the case. But observations made in our own laboratory, as well as by others, give no support to this view. Oat proteid, for example, isolated and purified was found no less readily utilized than that from lean meat or milk; and this corresponds with similar experience with other vegetable proteids. When, however, they are still mixed with the materials naturally associated with them, vegetable proteids are not ordinarily utilized to the same extent as those of animal origin.

In distinction from cereals and legumes, "vegetables," such as cabbage, beets, etc., are of little value as sources of proteid or fat, although the carbohydrates which they contain appear to be quite well digested and absorbed. Bryant and Milner conclude from their studies that "the chief value of many vegetables, however, is perhaps aside from the nutrients or energy they furnish; they add a pleasing variety and palatability to the diet, supply organic acids and mineral salts, and give the food a bulkiness that seems to be of importance in its mechanical action in maintaining a healthy activity of the alimentary tract. Possibly the result of these conditions is a favorable influence upon the digestion of other food eaten with the vegetable; at least such an effect was suggested by the results of some of the experiments. For instance, in the studies with potatoes and with apple sauce added to the basal ration the digestibility of the total ration including such material was noticeably higher than that of the basal ration alone."

Some of the fallacies frequently met with regarding these vegetable products are well illustrated in certain popular prejudices with respect to mushrooms, or edible fungi. They are generally regarded as constituting a very nutritious and sustaining diet; and this supposition has given rise to the extravagant statement that "a hearty meal on mushrooms alone would be about as reasonable as a dinner on nothing but beefsteak and might be expected to be followed by similar ill conse-

quences." Studies made in our laboratory, however, have indicated that the expression "vegetable beefsteak" is scarcely appropriate when applied to mushrooms in a strictly chemical sense. These fungi form no exception to the ordinary classes of fresh vegetable foods; indeed, they take a decidedly inferior rank in comparison with many. As dietetic accessories they may play an important part; but they cannot be ranked with the essential foods.

In this connection we may note the variable content of cellulose in some of the common articles of diet.

CELLULOSE CONTENT OF COMMON VEGETABLE FOODS (LOHRISCH).

	Per cent.
Spinach, as served.....	0.36
Head lettuce, uncooked.....	0.48
Kohlrabi, uncooked.....	0.73
Carrots, uncooked.....	0.74
Cabbage, uncooked.....	0.79
Cucumber, as served.....	0.11
Potato, dried.....	1.22
Potato, boiled.....	0.25
Potato, raw.....	0.21
Lentils, uncooked.....	3.39
Oatmeal, dry.....	0.24
Rye bread.....	0.15
Graham bread.....	0.94
Rademann's cellulose bread, dried.....	3.24
Cacao powder, dry.....	2.29
Agar-agar, dry.....	0.62

Systems of Diet.—From early times various systems of diet and dietetic cures have found favor and received vigorous advocacy from approving followers. Most familiar is vegetarianism, a system of living which teaches that the food of man should be derived directly from the plant world. Considered in the light of its history, however, vegetarianism involves something more than a mere dietetic program. It teaches that the use of animal foods is morally wrong as well as erroneous with respect to the processes of nutrition. But in view of the widespread advocacy of this exclusive régime, it may be worth while to consider the physiological aspects which the system presents. At the outset, it should be noted that a diversity of views has entered into the so-called vegetarian doctrines. The most radical reformers have abstained not alone from all food of animal origin but also from tubers and underground roots, eating only vegetables and fruits grown in the sunlight; others again reject cereals and live on fruits, nuts, and milk; while the most conservative exclude only fish, flesh, and fowl from their diet. Among the latter groups may be arranged the so-called fruitarians, who abstain from all food obtained by infliction of pain.

Among the more strictly scientific arguments advanced against the use of animal foods are those relating to the dangers of disease lurking in them. This applies chiefly to the flesh of animals; such foods as eggs, milk, and butter, all derived from animals, are not ordinarily excluded from the modern vegetarian dietary, but rather contribute thereto in considerable measure. It must be admitted that meat may be the carrier of harmful organisms, ptomaines, etc.; but this fact affords no funda-

mental source of objection to animal foods, since the dangers here alluded to are avoidable, and vegetable foods themselves are by no means free from similar objections. The high content of "extractive" substances—creatin, purin bodies, inorganic salts—in meat is also referred to as an undesirable feature of any ordinary animal diet. We have seen that these play a peculiar role in metabolism, failing in part to yield any energy to the organism, and again becoming partially oxidized to compounds like uric acid, which may have a significance in certain pathological conditions. On the basis of the facts now available, no serious objections against the small quantities of the meat bases daily ingested in an average dietary can be formulated for the healthy individual. Apparently they belong to the same category as many other food accessories such as tea, coffee, and alcohol, and are open to similar criticism. The supposed influence of meat extract in increasing the nutritive value of vegetable foods has not been substantiated. The substances which lend peculiar character to meat act in the same stimulating and refreshing manner that tea and coffee undoubtedly do, and from this standpoint must be looked upon merely as pleasant adjuncts to the food. Bunge writes: "That some organic constituent of meat-extract may produce an effect on the muscular or nervous system must be admitted to be remotely possible; at present it is in no way proved. We know, with regard to bouillon, absolutely no more than that it tastes and smells agreeably. This fact, however, suffices to explain all the 'enlivening' and 'strengthening' virtues which common experience attributes to extract of meat and bouillon, and to recommend them as valuable and pleasant accessories of our food."

We are inclined to believe that rational objections against a meat diet are applicable with respect to quantitative aspects rather than to the chemical make-up of such dietaries. In other words, it is the abuse of meat in modern dietaries which should be charged with any dangers attaching to the employment of this animal food; and the disadvantages of an excessive proteid diet apply with far less force to vegetarian régimes, owing to the proportionate nitrogen deficiency of the ordinary foods included in them.

An appeal to the characteristics of races or peoples accustomed to fixed types of diet is frequently made in support of the superiority or undesirability of different nutritive habits. Mental and physical peculiarities of classes living largely on rice or other cereals are contrasted with those of fish- and flesh-devouring tribes. It is widely believed that meat eating tends to develop a degree of aggressiveness and related traits of character, in distinction from the more pacific features of those nations accustomed to the extensive use of cereals in place of meats. This seems somewhat exaggerated; and to us it appears doubtful if temperaments or physical stamina are so directly controlled by dietetic habits. It is questionable, for example, whether Gautier is justified in contending that by depriving him of meat it is easier to debilitate an Englishman or a Dutchman than a Spaniard or Italian. The diverse dietetic customs of individuals and races have become established primarily by virtue of their peculiar environments, and the physiological features have developed only in a secondary way. In the case of carnivorous animals, the very traits which are referred to the flesh diet are

necessarily established in animals which must gain their food by preying upon others. Analogy may be most misleading in science.

A final argument in support of the vegetarian diet is based upon the supposed structural adaptation of the alimentary canal to such a régime. In reply it may be pointed out that a mixed diet is admirably utilized in man in the light of experimental evidence. There are no convincing physiological or anatomical grounds for recommending an *exclusive* diet of either animal or vegetable origin. The disadvantages attaching to the exclusive use of foodstuffs offering a large content of indigestible and unutilizable residues in the gastro-intestinal tract has frequently been urged against the vegetarian. Fruits and vegetables are extremely bulky in proportion to the available nutrients in them, and may entail considerable alimentary waste. In fairness, a sharp distinction must be drawn between vegetable diet and vegetarian diet; and with progress in the processes of commercial food preparation many improvements in adapting plant products for dietetic uses have been introduced. The palatability and nutritive value of cereals and nuts in particular have been enhanced by technical processes, so that many of the newer food products promise to compete actively for popular favor with animal foods.

If we attempt to separate fact from fancy in an estimate of the nutritive significance and possibilities of vegetarian diet, there can be no question regarding the actual *possibility* of sustaining life with foods drawn exclusively from plant sources. Careful studies of the metabolism of individuals living largely or entirely on such dietaries are available in sufficient numbers to demonstrate with scientific accuracy what familiar observations have long indicated. Nor can there be any question as to the possibility of sustained and vigorous muscular exertion by persons accustomed to a vegetarian régime. This is no more than might be expected, since it has been demonstrated that the essential source of energy liberated in muscular work is to be found in non-nitrogenous foods, the preponderance of which specially characterizes the vegetarian diet. There is, however, no evidence that the vegetarian utilizes his food better or works more economically. Where advantage accrues it is referable in greatest measure to the moderation in diet which the so-called vegetarian régime tends to encourage. The appetite is stimulated to a lesser degree than by meats and meat products, and this fact taken in conjunction with the usual more bulky character of vegetable foods diminishes greatly the tendency toward overeating. The practice of temperance in matters of diet may be facilitated by the introduction of vegetarian methods, thus contributing therapeutic possibilities applicable in the treatment of metabolic disorders related to overnutrition or similar perversions—gout, plethora, obesity, etc. There are idiosyncrasies in which vegetable as well as animal foods meet with difficulties in the way of practical use. One is inclined to emphasize the desirability of using common sense in the application of dietetic rules, remembering that man is well adapted by nature and experience to subsist on a variety of foods. On matters of diet every man should be a law unto himself, using judgment and knowledge to the best of his ability, reinforced by his own personal experiences. Vegetarianism may have its virtues, as too great indulgence in flesh foods may have its serious side; but there would seem

to be no sound physiological reason for the complete exclusion of any one class of foodstuffs, under ordinary conditions of life.

Diet "Fads" and "Cures."—Aside from the broader systems of diet already considered and many dietetic "fads" which have been exploited in a popular way, a goodly number of diet-cures, involving either extensive use or omission of certain types of food materials, have received the advocacy of the medical profession at times and thus found their way into the literature of nutrition. In illustration of some of the types here referred to, we quote actual dietaries which amply represent the characteristic features.

Dietary of a Fruitarian.—The subject was a man aged sixty-three years, weighing 124 pounds. He had lived upon a fruitarian diet for upward of twenty years, and, while he had at times used cooked vegetables and cereals, he believed that a diet of ripe and sweet fruits with nuts agreed with him best. During the experimental period of twenty days the subject walked from 4 to 8 miles a day, besides working a little at gardening. His average daily food intake, consisting almost exclusively of fresh fruits and nuts, contained proteids, 40 grams; fat, 54 grams; starch, sugar, etc., 286 grams; crude fiber, 25 grams; with a total fuel value of 1,700 large calories. The articles of diet used were cottage cheese, honey, apples, bananas, cantaloupe, four varieties of grapes, scarlet haws, pears, pomegranates, persimmons, oranges, strawberries, watermelon, dried figs, olive oil, almonds, and peanut butter. Though the data fall far below the tentative dietary standards, the individual was apparently able to satisfy his nutritive demands (Jaffa).

Dietary of a Vegetarian.—I. The subject, accustomed to only light exercise, was a healthy man, aged thirty-eight years, weighing 61 kilos, who was under observation in our laboratory for many months, during which he abstained from meat, fish, and eggs. His average daily output of nitrogen in the urine was 8.5 grams. A typical day's ration, selected from a period in which he was actually in nitrogen equilibrium, is the following:

Breakfast.—Oatmeal, 237 grams; butter, 10 grams; sugar, 35 grams; milk, 60 grams; coffee, 210 grams.

Lunch.—Macaroni, 142 grams; cheese, 10 grams; bread, 71 grams; sweet potatoes, 119 grams; milk, 250 grams.

Dinner.—Bread, 80 grams; butter, 20 grams; mashed potato, 176 grams; string beans, 77 grams; apple pie, 82 grams; milk, 250 grams.

Total nitrogen in the food..... 10.0 grams.

Total nitrogen in the urine..... 8.5 grams.

The estimated fuel value of food was over 2,000 calories.

II. Another individual of medium stature, observed by Caspari and Glaessner, after he had been accustomed to a diet *entirely* composed of plant products for many years, maintained nutritive equilibrium upon rations like the following:

	Nitrogen, grams.	Fat, grams.	Fuel value, calories.
20 grams, coffee.....	0.34	82
46 grams, sugar.....	182
330 grams, dates.....	1.49	927
113 grams, nuts.....	3.09	64.9	782
154 grams, oil.....	154.0	1,457
1,005 grams, potatoes.....	3.02	988
30 grams, carrots.....	0.33	136
Total.....	8.27	218.9	4,554

This case is of interest in view of the extensive introduction of fat into the dietary and the complete exclusion of butter, milk, cheese, or eggs. The food utilization was not as good as in case of subject I, living almost entirely on cooked, rather than raw products.

Dietary in "Proteid-Fat" Cures.—The elimination of carbohydrates from the dietary, with substitution of fats and proteids, has been recommended by clinicians for the dietetic treatment of certain maladies, principally diabetes and obesity. Without discussing here the disadvantages of such a selection as is usually made, with its preponderance of meat, we quote a typical recommendation by F. A. Hoffman:

Morning.—Milk, 200 grams; cream, 50 grams; two eggs; butter; meat, 100 grams.

Noon.—Meat, 200 grams; with peas or green vegetables.

Afternoon.—Milk, 200 grams; cream, 50 grams.

Evening.—Four eggs; ham.

The total fuel value is estimated at 2,200 large calories, and an increase in the proteid content is made possible by addition of preparations of pure proteid such as "plasmon" and "nutrose." Many of the dietaries now advised in tuberculosis resemble the above in various ways, with eggs added in larger quantity. In numerous instances, the phthisical patient is not noticeably injured thereby; nevertheless, it is doubtless wise to sound a warning of possible danger in this high proteid nutrition in such cases.

Dietary in "Hypernutrition" Cures.—As illustration of a typical dietary recommended in the "rest cure" introduced into medical practice by Weir Mitchell, the following maximal intake continued for four weeks has been adopted by Burkart. It should be remembered that the patients are inactive for the most part during the period of treatment.

	Quantity, grams.	Proteid, grams.	Fat, grams.	Carbohydrate, grams.	Calories.
Milk.....	2,064	70.4	75.0	101.0	1,296.0
Meat.....	352	59.8	7.0	502.2
Eggs.....	212	26.7	487.6
White bread.....	30	2.0	21.6	79.5
Zwieback.....	325	18.0	180.0	852.0
Potatoes.....	200	8.6	42.0	199.4
Vegetable.....	100	1.0	3.0
Butter.....	20	16.6	50.0	145.3
Sweets.....	100	3.0	0.5	15.0	80.0
		195.5	99.1	412.6	3,642.0

To the preceding list may be added such further extreme types of dieting as are represented in the so-called milk-cure, whey-cure, grape-cure, etc., in which a moderate diet is used containing a large proportion of the foods suggested by the names applied. Whatever therapeutic value they have is doubtless associated with a degree of moderation in eating which they induce, as well as with minor influences such as the mild diuretic and laxative effects incidental to the grape régime.

Artificial Food Preparations.—Modern times have witnessed the introduction of an almost endless number of food products prepared on a commercial scale by modifying the natural foods in various ways. The prevailing preferences and methods have been altered from time to time, in accordance with the changing attitude toward the products of the period. A few years ago the use of various types of “predigested” foods was hailed as an important advance in feeding methods. This was especially true of numerous albumose (proteose) and peptone preparations, which found their way into practice. The early favorable reception which these products received has, however, not been continued. Experiment has shown that they can, under appropriate conditions, replace true proteids in the diet without apparent disadvantage during brief periods of observation, and with maintenance of nitrogenous equilibrium. But in view of the manifold provision in the alimentary tract for the proper and complete digestion of proteid compounds, the unpalatable character of most of these predigested materials and the unfavorable symptoms (diarrhœas, etc.) which larger doses of concentrated soluble foods may induce, their popularity has gone. In place of them a variety of native proteids, some of them in the form of soluble salts, like the casein derivatives, has been brought into prominence. Similar considerations apply to the carbohydrate and fat foods, all of them being combined with alcoholic fluids to form widely used stimulant or “tonic” preparations. It is true that most of these are readily assimilated; yet it can scarcely be questioned that any therapeutic value which they may exhibit is attributable to their nutritive properties in minor degree only. Too frequently the “food-tonic” habit is induced in ways both irrational and unadvised. At present the field for artificial food preparations is more generally restricted to infant nutrition.

Artificial Nutrition.—The cases in which ordinary methods of nutrition cannot be applied because of some temporary or permanent disability of the ordinary paths of alimentation are sufficiently familiar to the physician. Artificial modes of nourishment in such instances have long been practiced in the form of feeding through a stomach tube, or of rectal feeding. It is in this latter process that the modern soluble food preparations promise to be of some value. Views regarding the ideal composition of nutritive enemata are somewhat at variance. The practice, however, is sufficiently well established to assure its usefulness. Subcutaneous injection of soluble foodstuffs has lately been advocated, especially by v. Leube in the use of fats. This author claims to have achieved a satisfactory absorption of liquid fats from under the skin, olive oil being employed. It is doubtful whether any satisfactory utilization occurs in this way. For proteids the experience on record is unfavorable, as might be expected, if a more complete break-down is essential to their proper metabolism. In the case of carbohydrates studies

in our laboratory have shown that compounds like glycogen, dextrin, inulin, and isolichenin are absorbed from beneath the skin, but excreted again in part unchanged in the urine, owing presumably to the lack of appropriate digestive enzymes to convert them into "physiological" sugars during their passage into and through the circulation. The variable fate of different sugars has been previously noted and although over 50 grams of *dextrose* can be introduced subcutaneously in man without excretion of the sugar, the practical difficulties encountered in infusing any considerable quantities of nutriment in this way are at present almost insuperable.

The increasing scientific and intelligent interest in the subject of nutrition is full of promise for the future. v. Leyden has well said: "The healthy and orderly conduct of our daily life is intimately associated with three important factors: nutrition, work, sleep. A measured participation in these closely interdependent things will preserve health, prolong life, and perfect the valuable habits of regularity, moderation, and self-control. Nutrition should therefore be looked upon as an important function—as a duty of man toward himself."

PART IX.

CONSTITUTIONAL DISEASES.

CHAPTER XXIX.

DIABETES MELLITUS.

By THOMAS B. FUTCHER, M. B.

Definition.—A disorder of carbohydrate and fat metabolism characterized usually by progressive loss in weight, thirst and polyuria, and by the persistent excretion of glucose in the urine while the individual is on a diet containing only moderate amounts of carbohydrates, or, in certain instances, even when no carbohydrates are ingested.

Historical.—Salomon and Hirsch have given the best historical accounts of the disease. Hippocrates made no reference to it in his writings. Celsus, in the first century, described a disease characterized by polyuria, wasting, and bodily weakness. Aretæus (circa 150 A. D.) was the first to use the term diabetes (διάβήτης, a syphon). He noted the thirst, diuresis, and the striking emaciation. The writings of Galen indicate that he was familiar with the main symptoms of the disease. The ancient Hindoo physicians of India are credited with having been familiar with the sweet taste of diabetic urine. This characteristic is said by Hirsch to have been described in the Ayur Veda of Susruta, written in the sixth century. In a Cingalese treatise of the fifteenth century, diabetic urine is referred to as “modu mehe” or *honey urine*. Notwithstanding these references to the sweetness of the urine, the credit for pointing out this characteristic is universally attributed to Thomas Willis, who described it in his “Pharmaceutice Rationalis,” published first in 1674. On page 71 of Pordage’s translation of this treatise, which appears in the 1684 edition of this author’s complete works, the following statement occurs:—“But as to what several Authors say, that the Drink is little or nothing changed, there is no truth in their suggestion; because in all People (that I ever happened to know, and I believe it to be so in all) their Urin was very different not only from the Drink that they took in, but also from any other humors that are usually generated in our Bodies, being exceedingly sweet, as if there had been Sugar and Honey in it.” It was not until 1776, a century later, that Matthew Dobson, of Liverpool, demonstrated that the urine contained saccharine matter, by evaporating down two quarts of diabetic urine and obtaining a cake of sugar weighing 2 oz., 2 dr., 2 scr.

He noted that the urine lost its sweet taste when it fermented, and also stated that the blood serum was sweet.

Rollo's advocacy, in 1797, of a meat diet in the treatment of diabetes, marks an epoch in its history. He was also the first to give a detailed and intelligent account of the disease. In 1849, Claude Bernard demonstrated that, in animals, puncture of a point in the floor of the fourth ventricle near the tip of the calamus scriptorius and between the nuclei of the pneumogastric and auditory nerves, causes a transitory glycosuria. In 1857, he discovered the glycogenic function of the liver. A great advance in our knowledge of the disease was furnished, in 1889, by Minowski and v. Mering, who demonstrated that complete extirpation of the pancreas in various animals regularly caused a permanent diabetes. In 1900, Opie and others pointed out the association between degeneration of the islands of Langerhans of the pancreas and the existence of glycosuria. The investigations of Otto Cohnheim, published in 1903 and 1904, and purporting to show that the carbohydrates of the system are normally burnt up by the interaction of glycolytic bodies formed in the pancreas and muscles, promise, if eventually confirmed, to go far toward elucidating many hitherto obscure points in the metabolism in diabetes mellitus.

Etiology.—I. Predisposing Factors.—Although diabetes is not a very common disease, a study of its *incidence* seems to indicate that it is on the increase in the United States, even allowing for the greater accuracy in diagnosis, and in the reporting of deaths in recent years. The United States Census for 1850 gave 0.9; for 1860, 1.2; for 1870, 2.1; for 1880, 2.8; for 1890, 5.5; and for 1900, 9.3 deaths from diabetes per 100,000 population. In the census year 1900, there were 4,672 deaths from the disease in the United States, of which 2,650 were in males and 2,022 in females. In this year the ratio of deaths from diabetes to the total number of deaths was 1 to 222. Statistics recently published by Tyson gave the ratio of deaths in Philadelphia, for 1900, as 1 to 402. In 1870, the ratio was less than half this, namely 1 to 850, thus indicating a marked increase in the prevalence of the disease. In Greater New York City, the death-rate from diabetes in 1900 was 10.3, and in 1902, 12.96, per 100,000 population. In Baltimore, the death-rate from the disease in 1900 was 8.3, and in 1903, 6.5, per 100,000. The incidence of diabetes in Baltimore is further indicated by the fact that in the seventeen years since the opening of the Johns Hopkins Hospital, ending May 15, 1906, there were 259 cases under treatment in the medical wards and medical section of the dispensary, out of a total of 106,000 medical patients. Of these, 159 were in-patients in the medical wards among 19,685 medical admissions or 0.8 per cent. of the total. The more recent statistics are opposed to the view that diabetes is much less frequent in the United States than in Europe. The report of the Registrar General for England and Wales, for 1900, gave 8.6, and for 1903, 8.5, deaths from diabetes per 100,000 population, while the rate in the United States for 1900 was 9.3. According to Saundby, writing in 1897, the death-rate from the disease per 100,000 population varies considerably for the different European cities and countries. In Paris the death-rate is 14; in Malta, 13; in Copenhagen, 7; in Vienna, 4; in Norway, 2; in Prussia, 2; and in Italy, 1.5.

Race.—The statement that diabetes is very uncommon in the colored race does not seem to be altogether borne out by facts. In the Johns

Hopkins Hospital series of 259 cases, there were 26 in negroes, or 10.03 per cent. Among the 159 ward cases, there were 143 whites and 16 colored patients, or a ratio of 9 to 1. The ratio of white to colored admissions in the medical wards during this period has been about 4 to 1. Thus, 1 out of every 10 cases of diabetes occurred in the colored race, while 1 out of every 5 medical admissions was a colored patient. Expressed in terms of susceptibility, it would appear then that in Baltimore the white population is only twice more liable to the disease than the colored. The United States Census report for 1900, on the other hand, gave only 48 deaths from the disease in the colored race out of a total of 4,672 deaths from diabetes. Of these 28 were in males and 20 in females. All authorities agree that the Hebrew race is particularly susceptible. Frerichs states that of his 400 cases, 102 were Jews. Wallach clearly demonstrated its greater frequency among the Hebrews of Frankfurt. From 1872 to 1890 there were 171 deaths from diabetes in that city. The proportion of deaths from diabetes to the deaths from all causes was six times greater amongst the Jews than amongst the rest of the inhabitants. The factors occasioning this greater susceptibility in Hebrews are not well understood. It has been variously ascribed to greater instability of the nervous system, fondness for sweets, and over-eating and sedentary habits amongst the better classes, particularly. Diabetes is very common among the educated and commercial classes in India, and Rose and Sen have shown that it is the Hindoos who chiefly suffer. The disease is said to be very uncommon in China and Japan.

Heredity, undoubtedly, is a factor in many cases. Several brothers and sisters may be affected. While one or other parent may have the disease, they often escape, and an uncle, aunt or cousin may suffer from it. Richard Morton, who termed the disease *hydrops ad matulam*, or dropsy of the chamber-pot (*Phthisiologia*, 1689), records a family in which four children were affected, one of whom recovered on a milk diet and diascordium. Pleasants found only 6 cases, or 5.3 per cent. with a family history of diabetes, in the first 112 diabetics in Osler's clinic at the Johns Hopkins Hospital, and reported a family in which two brothers, two sisters, an uncle, and a grand-uncle had the disease. Of particular value is the series reported by Fitz and Joslin in which especial inquiry was made and in which heredity was found to play a *role* in 23.8 per cent. Naunyn obtained a family history of diabetes in 35 out of 201 private cases and in only 7 of 157 hospital cases. Obesity is often a feature in these hereditary cases.

The possibility of one person contracting the disease from another by *infection* was first suggested by Schmidt, in 1890. Amongst 2,320 cases, he recorded 26 instances in which the disease appeared in apparently healthy persons, living in intimate association with diabetics. These were chiefly married females who contracted diabetes after nursing husbands suffering from the disease. These are the cases of so-called "conjugal diabetes." Oppler and Külz, in 1896, reported 47 married couples amongst 3,489 diabetic patients or 1 to 93.3, or 1.08 per cent. Senator, in the same year, stated that amongst 770 of his cases of diabetes, there were 9 instances, or 1.19 per cent., in which a man and wife suffered from the disease. For several years the writer has had a husband and wife, both diabetic, under his care. The wife was shown to be diabetic in

1899, and sugar was first detected in the husband's urine in 1902. Both patients are rather obese. When one eliminates the influence of heredity, worry, obesity, and dietetic conditions in these cases, little evidence remains to support the hypothesis that diabetes can actually be contracted by one individual from another.

No age is exempt from the disease, but most authors agree that the largest number of cases occur in the sixth decade, that is, between fifty and sixty years of age. The incidence as to decades in the Johns Hopkins Hospital series of 259 cases is shown in the following analysis:—

1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
4	14	25	43	68	75	25	5

It will be seen that the largest number of cases—75, or 28.9 per cent.—occurred in the sixth decade. These figures agree closely with those of Frerichs, Seegen, and Pavy, all of whom found the largest number of cases in the sixth decade, their percentages being 26, 30, and 30.7 respectively. Wegeli, in an analysis of 102 cases in children under sixteen years, found the age distribution to be as follows: under one year, 3; one to five years, 26; five to ten years, 31; ten to sixteen years, 42. Stern mentions a case in which a child was apparently born with glycosuria, and in which recovery took place in eight months.

Diabetes is decidedly more common in the male sex. The proportion of males to females affected is about four to three. In our series of 259 cases there were 151 males and 108 females. Of the 4,672 deaths from the disease in the United States in 1900, 2,650 were in males and 2,022 in females. This disproportion is not so marked in childhood and extreme old age, when the figures are more nearly equal. The incidence of the disease in the two sexes in the colored race is indicated by the United States Census figures for 1900. Out of 48 fatal cases in negroes for that year, 28 were in males and 20 in females, practically the same ratio as in whites. Statistics at the Johns Hopkins Hospital, on the contrary, show a striking preponderance of the disease in females in the proportion of two to one. Of the 26 cases in the wards and the out-patient department, 17 were in females and 9 in males.

In spite of the fact that the disease is often seen in its severest form among the poorer classes, it is undoubtedly more common in those of good *social position*. Not infrequently the onset of the disease is preceded by a history of fright, severe nervous strain, mental worry, and irritation.

Obesity plays a very important role. Diabetes occurs very frequently in persons who become very stout during middle life. Frerichs had 59 cases of obesity among 400 diabetic patients, or 15 per cent. It occurred in 30 per cent. of Seegen's and in 45 per cent. of Bouchard's cases. Women are liable to become stout at the climacteric period, and are particularly prone to become diabetic at this time. Diabetes occurring in fat individuals is termed "lipogenous diabetes." When diabetes occurs in obese persons of middle age it is usually of a mild type, and the prognosis is more favorable, the glycosuria disappearing on a rigid diet. The obesity usually precedes the glycosuria by several years. The fat diabetic is more commonly met with in private than in hospital practice. Occasionally obesity develops rapidly in young persons before the twentieth year.

These subjects may also develop diabetes, which is always of a grave type and rapidly leads to a fatal termination.

Universally admitted as this connection between obesity and glycosuria is, the nature of the relationship between fat and carbohydrate exchange is not at all well understood. Von Noorden is of the opinion that the obesity is an early symptom of the diabetic condition, and that it develops long before glucose makes its appearance in the urine. Owing to the belief that the obesity is caused by the diabetic condition, he has given it the name "diabetogenous obesity." He believes that in every case of true diabetes, not only the oxidation of carbohydrates, but also their conversion into fat, is restricted. He says that it is conceivable that there are cases in which at first the power to burn up the sugar in the organism is alone interfered with, while the conversion of carbohydrates into fat still goes on. Under these circumstances the working or muscle-cells of the body are richly bathed in a nutritive sugar solution; nevertheless they are starved because they cannot, or at least can only with difficulty, seize upon the sugar molecule, owing to deficient powers of oxidation. As a consequence there occurs a sort of tissue-hunger, which excites reflexly a sharper appetite and leads to the ingestion of a greater quantity of food. The latter results directly in an increased deposit of fat. According to von Noorden, such persons are diabetic, only they do not excrete sugar externally through the urine, but into the easily accessible layer of adipose tissue.

We might suppose that the prolonged excessive use of carbohydrate food would favor the development of diabetes. There seems no satisfactory evidence favoring this view, however. Cantani stated that the majority of his Italian patients subsisted largely on farinaceous food. He believed the diet was an important etiological factor. In Ceylon, also, where diabetes is common, large quantities of saccharine food are taken. The Chinese, on the other hand, rarely suffer from diabetes, although their diet consists chiefly of carbohydrates.

The metabolic disturbances underlying *gout* seem to favor the occurrence of diabetes. Grube, of Neuenahr, found that 16 out of 177 diabetic patients suffered from gout, and 23 had gouty parents (hereditary alternating gout). This proportion is probably unduly high owing to the fact that the waters at Neuenahr are especially recommended for the mild cases of diabetes occurring in gouty patients. Von Noorden says that the connection between the two diseases may manifest itself in various ways. The patient may suffer from typical attacks of gout in middle life, and later the attacks cease and glycosuria appears. On the other hand, cases are observed in which attacks of gout alternate with glycosuria (diabetes alternans). In a third group, gouty symptoms and glycosuria are present at the same time. In all these cases the diabetes is of a mild type and is compatible with a long life.

In occasional instances, diabetes may be traced to a *syphilitic infection*. The cases are undoubtedly rare. Feinberg reported 3 cases of diabetes and 1 of glycosuria which he attributed to a syphilitic infection. Where syphilis plays a part, the lesion is most probably a local one, and most likely to be situated in the region of the medulla. Nutritional changes in the brain and pancreas from syphilitic arterial disease must be considered as a possible cause for the diabetic manifestations.

In certain cases the diabetic symptoms have begun shortly after one of the *infectious diseases*. Cases have followed typhoid fever, scarlet fever, cholera, diphtheria, and rheumatic fever. There seems no satisfactory evidence supporting the view that malaria is a contributory cause. Williamson thought influenza played a part in 6 out of 100 cases in which special inquiry was made into the previous history.

In rare instances diabetes appears to be induced by *pregnancy*. The disease may manifest itself only during the pregnant period, being absent in the intervals. It is an occasional accompaniment of *Basedow's disease*. More often a transitory glycosuria occurs. Lowered tolerance to carbohydrates in this disease has been demonstrated by numerous observers. Falkenberg has reported cases in which glycosuria has followed extirpation of the thyroid. Marie, Fraenkel, Strümpell, and others, have observed it in *acromegaly*. A transitory glycosuria occasionally supervenes after attacks of *gall-stone colic*. It may occur after the administration of a general anæsthetic, and in other forms of narcosis. *Asphyxia*, occasioned by carbon monoxide or carbon dioxide poisoning, may cause a glycosuria, or even a true diabetes. In this connection also may be mentioned the glycosurias following the administration of certain drugs, such as amyl-nitrite, strychnine, curare, and methyldehlinin.

Glycosuria in Lesions of the Central Nervous System.—Although isolated observations had previously called attention to an association between certain lesions of the nervous system, and glycosuria or diabetes, it was Claude Bernard, who, in 1849, first demonstrated this relation by his celebrated "piqûre" experiment. He showed that by puncturing a point in the floor of the fourth ventricle, situated between the centres for the pneumogastric and auditory nerves, a hyperglycæmia, polyuria, and a transitory glycosuria occurred, lasting six hours in the rabbit, and about forty-eight in the dog. Although this experiment has not been confirmed in man, it is not surprising that certain injuries to the central nervous system cause sugar to appear in the urine. Thus glycosuria or a true diabetes may follow severe *trauma*. Ebstein obtained a history of external injury in 6 out of 116, and Williamson in 6 out of 100 cases of diabetes. Ebstein collected 50 cases of traumatic diabetes from his own clinic and from the literature. In one-half of these, the head was the seat of the injury. Glycosuria is more liable to follow trauma in this situation. In other cases, injuries to the neck, liver, kidney region, and pubes, have been followed by it. Ebstein thinks that individual predisposition is a large factor in determining the occurrence of diabetes in these cases. Glycosuria may also develop in the course of a traumatic neurosis.

Glycosuria or a true diabetes may occur in *organic lesions of the brain*, without Bernard's "diabetic centre" being necessarily involved. Glycosuria is not infrequent after *cerebral hemorrhage*. It rarely appears earlier than two hours after the apoplexy, and usually clears up within six days. Naunyn knows of only one instance where the glycosuria has passed over into a true diabetes—a case reported by Meyer. A true diabetes may be occasioned by a *tumor* of the pons, medulla, or cerebellum. Osler cites a case, seen with Reiss at the Friedrichshain, Berlin, of a woman with anomalous cerebral symptoms and diabetes, in whom at postmortem a *cysticercus* in the fourth ventricle was found. Ebstein reported 4 cases in which there was a coincident occurrence of *epilepsy* and diabetes, but

attributes the two diseases to the same cause. Similar observations have been made by Naunyn, Jacobi, and Lallier. Naunyn observed a case in chronic *encephalomalacia*. Observers agree in the comparative frequency of glycosuria, or a mild diabetes, in *general paresis*. Bond reports having found it in 10 per cent., and Strauss in 9 per cent. of their cases. Glycosuria is an occasional accompaniment of *tabes dorsalis* and *multiple sclerosis*. Tumors of the *vagus* and involvement of the nerve secondary to a caseated lymph-gland have been associated with a glycosuria. The latter is sometimes seen in severe cases of sciatica, but in this connection it must be remembered that neuralgias are not uncommon in diabetes. Isolated instances of disease of the abdominal *sympathetic ganglia* accompanied by glycosuria have been reported.

Experimental Pancreatic Diabetes.—Since Thomas Cawley, in 1788, recorded a case of diabetes in which the pancreas was atrophied and contained calculi, changes in the gland have been from time to time reported by clinicians and pathologists in this disease. In 1877, Lancereaux, on the strength of numerous clinical observations, described a special form of diabetes under the name of *diabète pancréatique ou diabète maigre*, in which emaciation was the striking feature, in contradistinction to *diabète gras*, in which the subject remains well nourished, and in which the pancreas was not thought to be involved. A great advance in our knowledge of the relationship between the pancreatic functions and diabetes resulted from the publication by Minkowski and von Mering, in 1889, of the results obtained from the extirpation of the pancreas in animals. These results have since been amply confirmed. Our knowledge concerning experimental pancreatic diabetes may be briefly summarized as follows: The complete extirpation of the pancreas in dogs, cats, pigs, carnivorous birds, frogs, and turtles, is regularly followed by a permanent glycosuria; and in dogs, particularly, the train of symptoms is almost identical with those of severe diabetes in man, and in a comparatively short time terminates in death of the animal. This result is not due to cessation of the flow of pancreatic juice into the intestinal canal, because diabetes does not follow when the duct is ligatured or when the juice escapes externally through a cutaneous fistula. When about one-tenth of the gland is left behind with power to functionate, the glycosuria is slight and occurs only when carbohydrates are ingested. When more than one-tenth of the gland is left behind in a functioning condition, diabetes does not result. That the diabetes is not a result of injury of the sympathetic nervous system, as some have claimed, is shown by the fact that when the pancreas is only partially extirpated, and the remaining portion, with the vessel intact, is transplanted into the abdominal wall, diabetes does not occur. If later this engrafted portion be removed diabetes quickly supervenes. It should be emphasized here that in experimental pancreatic diabetes the deposition of the glycogen in the liver and muscles is interfered with. The animals may be given abundance of starchy material without more than traces of glycogen being found in these organs. There is always a hyperglycæmia, however, the amount of sugar in the circulating blood reaching as high as 0.5 per cent. within twenty-four hours. Minkowski and von Mering formulated the following hypotheses: either some substance which has an inhibitory action on sugar conversion collects in the blood after extirpation of the pancreas, or else, after this oper-

ation, some substance is wanting or function abolished which, under normal conditions, serves to facilitate the conversion of carbohydrate bodies.

Lépine, of Lyons, in 1892, was the first to advance the view that diabetes in man, and after extirpation of the pancreas in animals, is due to the failure of the pancreas to produce a "glycolytic ferment," which occurs as an internal secretion. This hypothesis was based on the following experiments: When a quantity of blood of a normal dog is divided into two equal parts, one of which is heated to 54° C., and both then placed in a thermostat at 39° C., it is found that the amount of sugar in the unheated specimen is much less than in the other. That is, the ferment is destroyed in the latter, and glycolysis does not occur. When the blood of a pancreaticized dog, or of a human diabetic, was treated in the same way, the difference in the amount of sugar in the heated and unheated blood was much less, indicating the absence of the glycolytic ferment. These very suggestive experiments were not subsequently confirmed by the work of such investigators as Minkowski, Kraus, and Seegen.

Diabetes and Organic Diseases of the Pancreas.—It is not surprising, considering the foregoing experimental results, that pancreatic lesions in man are often followed by diabetes. Lesions of no other single organ so frequently give rise to the disease, and evidence is steadily accumulating to lead us to believe that many cases of diabetes, apparently unaccompanied by any organic lesion, are actually due to pancreatic disease made out only on microscopic examination. Most of the published statistics, showing the percentage of cases of diabetes with involvement of the pancreas, are altogether unreliable in the light of recent knowledge, owing to the fact that microscopic examinations were in the majority of instances omitted. According to Naunyn, a *pancreatic calculus* has been the most frequent lesion. Others would consider atrophy of the gland, *chronic interstitial pancreatitis*, the commonest pathological change. In the case of a calculus, it must be remembered that there is always an associated pancreatitis. Diabetes may occur when *cancer* involves the whole or greater part of the gland. It is an interesting fact that diabetes is absent in many of these cases. Hansemann, and Bard and Pic attribute the absence of the glycosuria to the assumption of the pancreatic function of the cancer-cells. It is surprising that glycosuria does not occur oftener in *acute hemorrhagic pancreatitis* with complete destruction of the gland. Seitz collected 100 such cases, in not a single one of which did glycosuria occur. This may be accounted for by the early death in most of these cases. Benda and Stadelmann reported a case with glycosuria. Sugar in the urine occasionally occurs in patients with *pancreatic cysts*.

The Association Between Diabetes and Lesions of the Islands of Langerhans.—The year 1900 marks a new epoch in our knowledge of the etiology of diabetes. In that year Opie¹ published from Welch's laboratory a pathological study on interstitial pancreatitis in which he for the first time demonstrated a connection between disease of the islands of Langerhans and diabetes. His results were published more in detail in the following year.² These groups of cells were first described by Langerhans, in 1869. They are composed of columns of cells having no

¹The *Journal of the Boston Society of Medical Sciences*, Vol. IV, p. 251, June, 1900.

²The *Journal of Experimental Medicine*, 1901, pp. 398-428 and pp. 527-540.

communication with the ducts of the gland, but being in intimate relation with a rich capillary network. They are about the size of a kidney glomerulus, measuring 0.2 mm. in diameter. The islands are situated for the most part in the centres of the ordinary gland acini, and are quite distinct, structurally and functionally, from them. They are distributed throughout the whole gland, but are more numerous in the tail than in the body or head. In tissues treated two or three days with Müller's fluid they appear, under low magnification, as conspicuous points of a bright-yellow color. With high magnification, they are found to be composed of small, irregular, polygonal cells having a round nucleus and homogeneous protoplasm.

Opie described two forms of chronic interstitial pancreatitis—an interlobular and an interacinar type. In the former, the development of fibrous tissue is most conspicuous between the lobules, while that within the lobules and between the acini is much less marked. In the latter, on the other hand, the interlobular connective tissue is not specially increased, whereas the connective tissue between the individual acini is markedly augmented. Here, also, the connective tissue may invade the individual acini when, as would be expected from their situation, the islands of Langerhans are likely to be involved. In his first series Opie reported 11 cases of the interlobular and 3 of the interacinar type. Of the 11 cases only 1 was accompanied by diabetes. In this case, the connective tissue had invaded the individual acini and had caused atrophy of the islands of Langerhans. Of the 3 cases of interacinar pancreatitis, 2 had diabetes, and the islands were extensively destroyed. In the third case it was thought that the absence of diabetes was due to the patient having died of typhoid fever before the islands had had time to become extensively involved. The most suggestive case of all was a girl, aged seventeen, who had suffered from diabetes for two years. The autopsy revealed no gross lesions to account for the disease. The pancreas, macroscopically, looked perfectly normal. On microscopic examination, however, it was found that the islands of Langerhans were completely destroyed throughout the whole gland, with practically no involvement of the ordinary secreting cells of the pancreas. In stained sections, the islands stood out conspicuously as red areas of hyaline degeneration—granular atrophy of Hansemann—a few nuclei still being seen, without any of the original island-cells being visible. Later, Opie observed 2 cases of diabetes with identical changes. This *hyaline degeneration* of the islands appears to be the characteristic lesion in cases of pancreatic diabetes in which they are not destroyed secondarily to an interstitial pancreatitis.

Ssobolew, working independently, published, in 1901, practically identical observations on the relationship between disease of the islands and diabetes. In view of the intimate association, in his series, between involvement of the islands of Langerhans and diabetes, Opie was led to conclude that there was a very intimate connection between the functions of these islands and carbohydrate metabolism. Laguesse and Schafer had previously suggested that the islands furnish an internal secretion in the same manner that the thyroid and adrenal glands do. Owing to the small size of the islands, and the almost utter impossibility of isolating them from the rest of the gland substance, it has been practically impossible to produce experimental evidence favoring this view, although

Ssoblew claims to have done so. Occurring as ductless glands, and being surrounded by a rich capillary network, it is extremely probable that these islands secrete some substance—we may call it a “glycolytic ferment” after Lépine—which enters the circulating blood, and which is necessary for the proper combustion of the carbohydrates in the system. Opie’s observations have been confirmed by numerous observers, among them, by Joslin in this country, and in Germany by Sauerbeck,¹ who has published the best review of our knowledge on the islands since Opie’s communication. Sauerbeck furnished a very important contribution to the subject by finding that ligation of the pancreatic duct in rabbits is eventually followed by diabetes, contrary to the view previously held. Until about the thirtieth day after the operation the islands of Langerhans are well preserved. On or about this day, however, they begin to disappear and their disappearance is marked by the simultaneous occurrence of sugar in the urine.

The theory that pancreatic diabetes is dependent upon disease of the islands of Langerhans, while generally accepted, has certain strong opponents, among them Hansemann of Berlin. There is every reason to believe, however, that very many of the cases of diabetes in which at autopsy no gross lesion is observable, will be shown to reveal degenerative changes in the islands of Langerhans when examined microscopically. Although it is probable that all cases of diabetes are not due to organic changes in these islands, we must keep in mind the possibility of a functional disturbance in the cases where organic changes are not demonstrable. It is quite likely that many of the cases of the so-called *endogenous diabetes*—that is, those without any attributable exciting cause, and without evident pathological lesions—are due to organic or functional disease of the islands of Langerhans. The recent work of Otto Cohnheim on the combustion of carbohydrates, to be referred to later, tends to support this view.

At this point also must be mentioned the interesting group of cases of “*bronze diabetes*,” occurring as a late manifestation of the remarkable affection known as *hæmochromatosis*. The latter condition is characterized by a peculiar pigmentation of the skin and viscera, associated with a form of hypertrophic cirrhosis of the liver and extensive sclerotic changes in the pancreas, and accompanied in the late stages by a persistent glycosuria. Hanot and Chauffard first described these cases, in 1882, and, in 1886, Hanot suggested the name *diabète bronze* for this type of diabetes, and, as he considered the liver changes secondary to the diabetic condition, he gave the name *cirrhose pigmentaire diabétique* to this form of cirrhosis. The true nature of the affection was first revealed in 1889 by von Recklinghausen, who described the disease under the name of *hæmochromatosis*. He showed that the pigmentation of the skin and viscera is due to the deposition of an iron-containing pigment, hæmosiderin, and a non-iron-containing pigment, hæmofuscin, in the tissues.

According to the latest conception of the disease, hæmochromatosis is to be considered as a primary affection of the blood in which the red cells are made more vulnerable, causing them to disintegrate more readily and to give up their hæmoglobin. The hæmosiderin possesses a brown color

¹ *Ergebnisse der Allgemeinen Pathologie und Pathologischen Anatomie*, Achter Jahrgang, II, Abteilung, 1902. Published in 1904.

and is deposited mainly in the cells of the liver, pancreas, lymphatic and sweat glands. The hæmofuscin, on the other hand, is finer, of an ochre-yellow color, and is present in the smooth muscle fibers of the stomach, intestines, blood- and lymph vessels, and occasionally in those of the urinary bladder, ureter and vas deferens. Hess and Zurhelle have recently made very careful studies of two cases of "bronze diabetes," that is, two cases of hæmochromatosis which had advanced to the diabetic stage. As a result of their chemical and histological studies they incline to the view that the cirrhosis of the liver and the formation and deposition of the pigment are dependent upon some common cause. They hold that some toxic substance, possibly alcohol, causes disturbances in metabolism which bring about the above changes. A lipæmia, which was present in one of their cases, is explained in the same way. Their investigations also go to show that a sharp distinction between hæmosiderin and hæmofuscin cannot be made. They claim to have found them side by side in the same cell with gradual transitions from one into the other. The hæmoglobin of the blood is in all likelihood their common source. As a result of the local deposition of the pigment in the liver and pancreas, a chronic interstitial inflammation occurs, producing in the case of the liver, a hypertrophic pigmentary cirrhosis, and, in the case of the pancreas, an interstitial pancreatitis of a pigmentary type. In the early stages or early years of this affection sugar does not appear in the urine, and it is only when the changes in the pancreas become so advanced that presumably the islands of Langerhans are largely or completely destroyed that diabetes develops. Whenever hæmochromatosis, either with or without diabetes, is suspected, the correctness of the diagnosis *intra vitam* will be made much more probable by removal of portions of the pigmented skin and the finding of iron-containing pigment in the cells of the sweat glands, by the potassium ferrocyanide test, and of the ochre-yellow hæmofuscin in the muscle fibers of any bloodvessels that may be present.

Naunyn, Grube, Laache, and Fleiner, have drawn attention to the frequency in the association between *arteriosclerosis* and diabetes. Nutritional changes in the pancreas, due to sclerosis of the pancreatic arteries, has been suggested as the assignable cause. Fleiner reported a case of diabetes in a patient with general arteriosclerosis in which there was a diffuse interstitial pancreatitis with marked thickening and obliteration of the branches of the pancreatic artery.

Diabetes and Organic Diseases of the Liver.—When one considers what an important part the liver plays in carbohydrate metabolism—being the great glycogen reservoir—it would be natural to expect that organic lesions of the liver would frequently be the cause of diabetes. Clinical experience, however, teaches us that the most extensive disease of the liver, such as carcinoma and cirrhosis, may occur without even a glycosuria occurring. Naunyn seems to be the strongest advocate of what he terms a "liver diabetes," that is, where the diabetes is due to the organic change in this gland. He describes personal observations of cases of diabetes attributed to *cirrhosis* of the liver and to the liver disturbances accompanying *gall-stones*. He also draws attention to the frequency with which he has met the glycosuria in individuals with enlarged livers, caused by *passive engorgement* secondary to cardiac disease. There does

not seem to be sufficient evidence at the present time to justify the opinion that a true "liver diabetes" exists. Until a larger number of cases of diabetes with organic disease of the liver and without microscopic evidence of disease of the islands of Langerhans are reported, we must support this contention.

Renal Diabetes.—The only cases known to be definitely of renal origin are those of "phloridzin diabetes," experimentally produced by the administration of phloridzin. The latter is a glycoside obtained from the bark of the trunk and root of apple, pear, plum, and cherry trees. In 1886, von Mering discovered that when phloridzin is administered by mouth or subcutaneously in man or animals, a temporary glycosuria results. The amount of sugar may reach 18 per cent. in dogs. The glycosuria continues in animals fed on nitrogenous diet, or in men when fasting, indicating that the sugar is in part manufactured from proteids. An important fact is that no hyperglycæmia exists. That the glycosuria results from the phloridzin causing certain changes in the renal cells rendering them more permeable to glucose, is indicated by the fact that there is no increase of glucose in the blood; by failure of a hyperglycæmia to occur after ligaturing the ureters or excising the kidneys; and by the observation of Zuntz, who found that when phloridzin is injected into one renal artery, glucose is excreted by the corresponding kidney immediately, while it does not appear in the urine of the opposite kidney until half an hour later, that is, until after it reaches that kidney through the general circulation.

Considerable doubt exists as to whether, clinically, the "renal diabetes" of Jacobi actually occurs. The instances of diabetes occurring in the course of chronic nephritis are usually cited in support of the view that a renal diabetes actually exists. Klemperer records a very suggestive case in which a patient with chronic nephritis excreted 0.35 per cent. of glucose. There was no accompanying hyperglycæmia, nor did the latter occur even after the individual was fed on bread and glucose and excreted as much as 150 grams of sugar daily. In fact the blood showed a hypoglycæmia. Naunyn reports 3 cases of diabetes in chronic nephritis, and inclines to the view that cases of renal diabetes occur, but admits that the question is still an open one. He cites the cases of glycosuria accompanying renal hemorrhages and chyluria, in support of the "renal diabetes" hypothesis.

Adrenalin Glycosuria.—There is no clinical or pathological evidence showing that diabetes bears any intimate relationship to disease of the adrenal glands. In rare instances, glycosuria has been found in association with lesions of these glands. Experimentally, however, it has been shown that adrenalin, the active principle of the gland, has a powerful influence on carbohydrate metabolism. In 1901, F. Blum reported the results of his experiments in connection with adrenal diabetes. He found that the subcutaneous injection of an aqueous extract of the adrenal gland produced glycosuria in 22 out of 25 dogs experimented upon. This observation was later confirmed by Suelzer and Croftan. Herter, in 1902, published his experiments with adrenalin chloride. He used a 1 to 1,000 aqueous solution of adrenalin chloride in his research. Subcutaneous, intravenous, and intraperitoneal injections of the drug in dogs were almost invariably followed by glycosuria. Peritoneal injections, other things being equal, produced the most marked glycosuria, an excretion of 10

per cent. or more of sugar not being uncommon. The glycosuria lasts usually a little over twenty-four hours. In order to ascertain whether the more marked glycosuria following intraperitoneal injection was due to the direct action of the drug on the pancreatic gland, the pancreas was exposed in a number of normal dogs, and adrenalin chloride solution was applied directly to the presenting surface of the gland. It was shown that a marked glycosuria followed the application of very small quantities of adrenalin to the gland—quantities which, when applied locally to other parts of the body, gave rise either to no sugar excretion or only a trivial glycosuria. The problem now to determine was just how this glycosuria is produced. It was first shown that it was not due to vascular disturbances. Owing to adrenalin chloride being a very active reducing substance, Herter thought that the glycosuria resulted from interference with oxidation within the pancreatic cells. Accordingly local applications to the pancreas of other reducing substances were made. Solutions of potassium cyanide constantly produced a glycosuria. Similar results were obtained with sulphurous acid, ammonium sulphide, sulphuretted hydrogen, illuminating-gas, carbon monoxide, and other reducing agents. Negative results were regularly obtained with non-reducing substances such as sodium chloride, sodium hydroxide, ferric chloride, hydrochloric acid, bromine water, etc.

Herter concluded that adrenalin chloride and the other reducing substances cause glycosuria by their power of removing oxygen from the pancreatic cells, thus interfering with their function. Histological examination of the pancreatic gland at the height of the glycosuria showed no recognizable lesion. He did not think that the glycosuria was due to loss of function of the islands of Langerhans, although, later, he found that fatal doses of adrenalin produced marked granular degeneration of the cells composing the islands. Herter considered the experiments of clinical importance in that they probably threw considerable light on certain forms of human glycosuria. He suggests that the forms of glycosuria following conditions of asphyxia, as after epileptiform seizures and carbon monoxide poisoning, may be due to interference with oxidation in the pancreas.

View that Diabetes is Produced by a Circulating Toxin.—In 1900, Hans Leo published the results of his experiments which led him to believe that diabetes was due to some unknown toxin. The urine from diabetic patients was found to cause glycosuria in dogs when administered by mouth and subcutaneously. This result was obtained with fermented as well as with unfermented urine. Leo was unable to determine the true nature or source of this toxin. That it was not of the nature of a ferment he concluded from the fact that it was soluble in water and alcohol, was not precipitated by oxalic acid, and not destroyed by heat. No proof has since been advanced to support Leo's view.

It is of interest to note that Hofmeister has produced a so-called "hunger-diabetes" in dogs by cutting off all food for several days. If a dog weighing two to three kilograms be then given 10 to 30 grams of starch, a glycosuria reaching 3.84 per cent. and a total excretion of 30 per cent. of the ingested starch results. So far as we know, an analogous condition does not occur in man; but Naunyn makes the suggestion that some of the glycosurias occurring in various cachetic diseases may be an expression of a hunger diabetes.

II. Disturbances of Metabolism in Diabetes.—The immediate cause of diabetes is the development of a hyperglycæmia; that is, an excess of glucose in the circulating blood. The explanation for the occurrence of this hyperglycæmia is the problem which has occupied the attention of so many investigators and one which is still in need of a solution.

As the metabolic disturbances in diabetes have to do mainly with the warehousing of the carbohydrates, they will probably be best appreciated by first reviewing the fate of the carbohydrates in normal metabolism.

The hexoses mainly concern us in a discussion of both normal and pathological carbohydrate metabolism. The hexoses, in general terms, may be described as carbohydrates, the molecules of which contain the carbon atoms to the number of six or multiples thereof, and the hydrogen and oxygen atoms in the proportion in which they form water. They are classified according to the number of carbon atoms they contain, as follows:

1. The *monosaccharides*, or *glycoses*, having the general formula $C_6H_{12}O_6$. These include grape-sugar, also called dextrose or glucose (dextro-rotatory); fruit-sugar or levulose (levo-rotatory); galactose and mannose (both dextro-rotatory). All these ferment and reduce alkaline copper-sulphate solutions.

2. The *disaccharides*, or *saccharoses*, possessing twelve atoms of carbon in the molecule, and having the formula $C_{12}H_{22}O_{11}$. These are formed by the combination of two molecules of a monosaccharide with the loss of a molecule of water. They include cane-sugar or saccharose; milk-sugar or lactose; and maltose. With the exception of cane-sugar, all reduce alkaline copper-sulphate solutions. All are dextro-rotatory, but do not ferment without being split up by dilute mineral acids, etc.

3. The *polysaccharides*, or *amyloses*: these are the anhydrides of a combination of many molecules of monosaccharides, and possess the general formula, $(C_6H_{10}O_5)_n$. They include starch, glycogen, and dextrin, (all dextro-rotatory); inulin (levo-rotatory); cellulose; and animal gum (inactive). They do not reduce alkaline copper-sulphate solutions and do not ferment without being previously split up.

Normal Carbohydrate Metabolism.—The carbohydrates in the food undergo a series of changes during digestion, as a result of the action of the diastatic ferments in the saliva, pancreatic juice, and succus entericus. Possibly some changes also occur in the process of absorption. Starch, the most abundant article in our dietary, is eventually converted into maltose, or maltose and dextrin, after passing through a series of intermediate stages. The maltose and dextrin are further converted into dextrose by the sugar-splitting enzymes of the intestinal mucous membrane. Cane-sugar, the sugar for ordinary sweetening purposes, is hydrolized into dextrose and levulose, and milk-sugar probably undergoes a similar change to dextrose and galactose, although of this we are not so certain. According to our present knowledge we may say that the carbohydrates of our food are eventually absorbed in the form mainly of dextrose (glucose) or dextrose and levulose. These sugars are absorbed directly into the portal capillaries and not into the lymphatics. As a result of carbohydrate digestion the portal vein conveys to the liver a stream of sugars consisting mainly of dextrose, but also of smaller quantities of levulose

and galactose, and there, by a process of dehydration, the liver-cells convert them into glycogen as follows: $C_6H_{12}O_6 - H_2O = C_6H_{10}O_5$. After the ingestion of carbohydrates, the surplus that is not required for the immediate use of the economy is stored up in the liver as glycogen. According to the generally accepted view of physiologists, this glycogen is reconverted into glucose, probably by the action of a special enzyme produced by the liver-cells. This glucose reaches the general circulation by the hepatic veins, and is conveyed to the tissues, where it is oxidized, producing heat and energy. This glycogenic function of the liver was first demonstrated by Claude Bernard, in 1857, and is generally accepted by modern physiologists, though it has been vigorously opposed in certain quarters.

Pavy and his followers differ from most physiologists in their views concerning the method of absorption of carbohydrates. He thinks that in health a considerable portion of the carbohydrates ingested is converted by the villi of the intestinal mucous membrane into fat and carried thence by the lacteals to the blood. Another portion is split up, being incorporated with nitrogenous material and carried away in the form of proteid. These changes are affected by the same cells of the villi. Pavy thinks that only the carbohydrates not thus assimilated as fat or proteid-carbohydrate pass to the liver and are there converted into glycogen in the manner described. "The office of the liver," according to Pavy, "is thus supplementary to the assimilative work performed elsewhere. If the latter work is efficiently performed none is left for the liver to accomplish. It is the sugar that is permitted to reach the portal vein that is taken up by the liver and it may happen that none reaches it in health."

Glucose and glycogen are formed not alone from carbohydrates, but a certain amount is manufactured from ingested and sometimes from body proteid. Evidence favoring this view was advanced by Claude Bernard, who showed that the liver of an animal kept under conditions ordinarily favoring the disappearance of the glycogen, such as fasting, exercise, etc., still contains glycogen when fed on an exclusive proteid diet. Further evidence is afforded by the fact that severe diabetics often excrete sugar when on a similar diet. According to Minkowski, 45 grams of carbohydrate is formed out of every 100 grams of proteid decomposed in the body. The general belief, however, is that in normal metabolism carbohydrates are probably not manufactured from the ingested proteids. In the disordered metabolism of diabetes, on the other hand, both the proteids of the food and particularly the body proteids yield considerable quantities of glucose.

The liver is capable of storing up glycogen to the extent of 14 per cent. of its own weight. The amount it contains depends on several factors. Prolonged fasting, continuous physical exertion, and high temperature, rapidly deplete its supply of glycogen. The latter is greatest in amount on a diet rich in carbohydrates. The liver is not the only seat for the storage of glycogen, however. The other great reservoir is the muscular system; and it is estimated that the quantity in the muscles practically equals that stored in the liver. When conditions favor the depletion of the supply of glycogen it is found that the muscles give up their supply much less readily than does the liver. The source of the muscle glycogen is not definitely known, but presumably it is formed from the glucose brought to the muscles by the circulating blood.

It has been clearly shown that the amount of glucose in the circulating blood normally varies within quite narrow limits, namely, between 0.1 and 0.2 per cent. This is remarkable because we would expect that when carbohydrates are ingested in large quantities the blood would contain more glucose than when they are taken in smaller amounts. This is not the case, however, for the percentage of sugar in the circulating blood remains in normal individuals constantly within the narrow percentage limits mentioned above. This naturally leads us to consider the fate of the carbohydrates under conditions which may be considered as normal variations.

(a) *In Ordinary Nutrition.*—In a healthy person, on a usual mixed diet and taking a moderate amount of exercise, the carbohydrates are always on hand and are always in demand. By their combustion, presumably for the most part in the muscles, they produce heat and energy. Owing to the fact that normally there is no loss of sugar in any of the excretions, excepting in the urine in the minutest traces, and owing to the interposition of the two carbohydrate reservoirs, the liver and muscles, the percentage of glucose in the circulating blood remains practically constant. After a meal the excess of carbohydrates is temporarily stored up in the liver as glycogen.

(b) *When the Supply of Carbohydrates is Insufficient and the Demand Excessive.*—For a few hours or days under these conditions the glycogen in the liver and muscles is called upon, and makes up for the deficiency of the carbohydrate intake. In this way the percentage of glucose in the circulating blood is kept within normal limits. Eventually the glycogen is entirely used up, yet the blood contains the normal amount of glucose. This has been thought by some to be due to the conversion of the body-fat into glucose. This view has few adherents, however, and the phenomenon is more likely explained by the conversion of the body-proteids into glucose.

(c) *When Carbohydrates are Ingested in Excess of the Needs of the Body.*—The fate here depends on circumstances. Within certain limits, the excess in carbohydrates can be stored up in the liver and muscles as glycogen. The limit of this storage capacity is eventually reached, for von Noorden states that the human organism is capable of storing up only about 300 grams of glycogen. Results will now vary according to whether the carbohydrates are ingested in moderate excess over a considerable interval, or in enormous quantities in a short period of time. In the former case the excess of carbohydrates is converted into fat which is deposited in the connective tissues, and no hyperglycæmia occurs. When, however, there is a sudden ingestion of an enormous amount of carbohydrates, the liver and muscles cannot store it all up as glycogen, nor can the organism convert it all into fat. An excess of glucose accumulates in the circulating blood. When the blood contains more than 0.2 per cent. of glucose a hyperglycæmia exists, which always results in the appearance of glucose in the urine.

The form of glycosuria produced in the manner just described is known as *alimentary glycosuria*. This may be considered a physiological process, and must not be confused with true diabetes. The quantity of sugar that can be ingested without its appearing in the urine is designated by Hofmeister as the *assimilation limit*. This varies in normal persons

according to the individual and according to the sugar ingested. Von Noorden states that the sugar that appears in the urine is the same as that ingested. This statement must be accepted with reservations. The glycosuria thus produced is known as *glycosuria e saccharo*. The assimilation limit for normal individuals on a fasting stomach is stated by von Noorden to be as follows: For milk-sugar, 120 grams; for cane-sugar, 150 to 200 grams; for fruit-sugar, 200 grams; for grape-sugar, 200 to 250 grams. When the sugars are taken after a light meal the limit is higher. It is well to emphasize here that, in a healthy person, sugar never appears in the urine after the ingestion of even enormous quantities of starch. Digestion and absorption take so much time that a sudden flooding of the blood with carbohydrates cannot take place. When a glycosuria does occur after the ingestion of starch it is called *glycosuria e amylo*. It should always lead the physician to suspect that a true diabetic condition exists, for it means that the assimilation limit, or power to warehouse carbohydrates, is lowered.

Manner in Which the Carbohydrates are Oxidized in the System.—We have until a recent date been almost entirely in the dark as to how and where the glucose of the blood is ultimately burnt up. At one time it was thought that it was oxidized in the lungs. Subsequently, the body tissues, particularly the muscles, have been held to be the seat where the carbohydrates are oxidized, yielding energy and heat, and resulting in the production of carbonic acid and water. Lépine and Barral held that this "glycolysis" was affected through the agency of a glycolytic ferment produced by the pancreas as an internal secretion. Arthus denied the existence of such a ferment in the circulating blood, and held that the enzyme is merely a postmortem product resulting from the disintegration of the red blood corpuscles.

Otto Cohnheim,¹ in 1903 and 1904, published the results of experiments which, if ultimately confirmed, seem destined to solve the mystery of carbohydrate metabolism, and to throw much light on the etiology of diabetes mellitus. By means of a specially constructed press, he obtained quantities of juice from the pancreas and muscles of cats and dogs. With each of these juices he first experimented separately. Each juice when added to a solution of glucose was inactive. When, however, muscle-juce and glucose-solution were mixed together, and then the juice of the pancreas added, there was a rapid, and eventually, a complete conversion of the glucose into carbonic acid and alcohol. Cohnheim holds that the ingested carbohydrates are burnt up in the muscles. He suggested two possible explanations for the remarkable results above noted. One is based on Ehrlich's side-chain theory. According to this view, the pancreas and muscles provide complementary and intermediate bodies, both of which are necessary for normal carbohydrate metabolism. His second explanation is in accord with Pawlow's findings regarding the relationship between trypsinogen, the proteid enzyme of the pancreas, and proteid digestion. Pawlow found that trypsinogen itself was inactive on proteids, but when it came into contact with the "enterokinase" of the intestinal juice it was converted into trypsin and then caused rapid digestion of the proteids. Cohnheim believes that both the pancreas and the muscles produce substances which are necessary for normal carbohydrate metabolism.

¹ *Zeitschrift für Physiologische Chemie*, Bd. XXXIX, p. 338, und Bd. XLII, p. 401.

He at first thought that these substances were of the nature of enzymes or ferments. According to this hypothesis, he held that the muscles produced a proenzyme which requires the action of a ferment, produced by the pancreas and contained in its internal secretion, before it can become active on carbohydrates. Cohnheim in his second communication gave the results of his experiments as to the nature of the glycolytic body produced by the pancreas. He found that it withstands boiling, is soluble in water and 96 per cent. alcohol, but insoluble in ether. For these reasons, he believes that the glycolytic agent of the pancreas is really not a ferment, but a body very closely allied in its characteristics to such other well-known constituents of internal secretions as adrenalin, iodothyron, and secretin. An interesting feature is that an excess of this body hinders, and, when present in large quantities, absolutely prevents, carbohydrate combustion. The most active sugar destruction occurs when muscle and pancreas are mixed together in the proportion of 75 grams of the former to 0.8 grams of the latter. When more than 0.8 grams of pancreas is added the activity diminishes, and ceases when 2 grams is reached. Cohnheim suggests two explanations for this remarkable finding. The first is, that the pancreas produces two substances, one of which favors and the other hinders sugar combustion. For various reasons he sets this aside as a possible explanation. The second is based on the observation of Neisser and Wechsberg, that the destruction of bacteria by a bacterial serum is due to the combined action of amboceptors and complements, and that an excess of amboceptors destroys the bactericidal action of the serum. By analogy, he suggests that by adding an excess of pancreas juice to a mixture of sugar solution and muscle juice, an overabundance of amboceptors is provided, thus destroying the glycolytic action of the two juices.

Rahel-Hirsch, whose researches were published practically at the same time as Cohnheim's, reached almost identical results. He found, further, that liver juice, preserved in toluol, itself caused an appreciable destruction of glucose in solution, but that the destruction was much more marked after pancreas juice was added.

Claus and Embden, in a publication which appeared early in 1905, stated that they failed to confirm Cohnheim's results. They believed that the sugar destruction in Cohnheim's and Rahel-Hirsch's experiments was dependent upon bacterial action and due to their failure to prevent bacterial growth in the added pancreas juice. Cohnheim claimed that their failure to confirm his results was due to defective chemical technique. In March, 1906, he published his results of a reinvestigation of his former work, and states that they entirely confirmed his early experiments. His theory is an extremely suggestive one. According to his view, the sugar of the blood is burnt up in the muscles through the agency of a glycolytic substance which results from the interaction of bodies produced in the pancreas and muscles. The bearing of this conception on carbohydrate metabolism in diabetes will be considered under the theories as to the causation of diabetes.

Having reviewed the main features of carbohydrate metabolism in health, it is now in order to see what variations occur in diabetes mellitus. Hyperglycæmia, or excess of glucose in the blood, is the most constant and striking evidence of disordered metabolism in the disease. Naunyn

states that he knows of no case of diabetes in man without a hyperglycæmia, with the exception of Klemperer's case of diabetes in chronic nephritis, where the glucose in the blood was said to be subnormal. It will be recalled that this case was cited by Klemperer as evidence in favor of a "renal diabetes." In phloridzin diabetes, which is a true renal diabetes, there is no hyperglycæmia, and often the glucose in the blood is decidedly below normal. The great problem is to ascertain why this hyperglycæmia occurs. Whereas the blood normally contains about 0.1 per cent. of glucose, with 0.2 per cent. as the maximum normal amount, in diabetes the glucose may reach 0.6 per cent. according to determinations made by Pavy and by Seegen. Naunyn found 0.7 per cent. in one case. This is among the highest percentages recorded.

Another very striking and almost constant metabolic disturbance in diabetes is the failure of the liver to store up glucose in the form of glycogen (zoöamylon), a condition to which Naunyn has given the term "dyszoöamylie." The amount of glycogen in the liver is usually reduced, or it may be entirely absent. Naunyn says that the evidence at hand is not sufficient to decide the question as to whether the deficiency of the liver in glycogen is due to failure of the liver-cells to convert glucose into glycogen, or mere failure of the liver-cells to store it up when received. This poverty in glycogen is also a striking feature in the experimental glycosuria following medullary puncture and extirpation of the pancreas. It is an interesting fact that a diabetic can store up glycogen in his liver from ingested levulose, whereas there is no conversion from ingested glucose. This failure of the liver-cells to store up glycogen is very closely related to the production of the hyperglycæmia. Why this power is lost is not yet understood. The fact that it occurs after extirpation of the pancreas in animals suggests the possibility that some ferment, contained in an internal secretion of the pancreas, is necessary to enable the liver-cells to form glycogen from ingested carbohydrates.

The metabolic disturbance in diabetes does not in itself cause an increase in the destruction of body proteids. The diabetic nearly always excretes a marked excess of nitrogen in the form of urea. This increase is due, however, in large part to the excessive ingestion of proteids, and must be considered physiological. The healthy individual would excrete proportionally large amounts of nitrogen if his diet were increased to the same extent. The condition becomes pathological only when the amount of nitrogen in the urine exceeds that taken in the food; in other words, when, in addition to the albumin in the food, that of the tissues also is decomposed. This occurs in diabetics when so much sugar is excreted that after the subtraction of its heat-value from the heat-value of the food, the latter is found to be insufficient. This waste of nitrogen is the greater the more the food value is depreciated by glycosuria. It is very large as long as the diabetic is left to himself to ingest the carbohydrates which are useless to him, but becomes slight or ceases when the diet consists largely of proteids and fat. In the severe cases of diabetes with rapid emaciation there is often a marked increase in the excretion of nitrogen, owing to the consumption of the body proteids.

It is not alone the metabolism of the carbohydrates that is disturbed in diabetes. It is only in the last few years that students of this disease are awakening to the fact that there is also a marked disturbance in fat

metabolism. There is now practically conclusive evidence that the power of the tissues to oxidize the fat of the food and body is markedly lowered. In the last five years evidence has gradually accumulated to show that β -oxybutyric acid and its derivatives, diacetic acid and acetone, arise as a result of the incomplete oxidation of fat. This is the generally accepted view as to their origin at the present time. It will naturally be inferred that, in the regulation of the diet of diabetics, we must not only consider the carbohydrates, but we must pay more attention to the prescribing of the amount and kind of fat than we have been accustomed to do heretofore.

Diabetes is sometimes considered among the auto-intoxications. We have no proof that an excess of glucose in the circulating blood is capable in itself of producing any toxic symptoms. Diabetic coma, the most serious complication of the disease, however, is definitely due to an acid auto-intoxication, as we shall see later on.

Theories of Diabetes Mellitus.—The results of researches published up to the present do not warrant any dogmatic statements as to the cause or causes of the hyperglycæmia in diabetes. We can conceive of its being occasioned in at least two ways: (1) By over-production of glucose. (2) By under-consumption of glucose in the tissues.

1. Theory of Over-Production.—There is no evidence to show that the diabetic individual forms any more sugar from a certain amount of food than does a healthy person from the same amount of food. We have instances of over-production in those cases of glycosuria, or true diabetes, resulting from irritation or injury to the nervous system, of which the medullary puncture is a type. In these cases, however, the over-production of glucose is a temporary one, and results merely from an over-production of glucose from the stored-up glycogen in the liver. Two explanations are given for the hyperglycæmia in these cases. One is that the injury to or disease of the nervous system causes a centripetal nerve-impulse to be sent out to the liver, causing its cells rapidly to part with their glycogen in the form of glucose. The other is that vasomotor disturbances are produced which result in increased vascularity of the liver. In this way a greater amount of some—as yet undetermined—ferment in the blood reaches the liver, causing a more rapid conversion of glycogen into glucose. Naunyn believes that the hyperglycæmia is directly dependent on the fact that the liver and muscles of the diabetic are unable to store up glycogen in the same way that they do in health. The glucose derived from the ingested carbohydrates and proteids goes to the liver, and, instead of being there temporarily stored up as glycogen until required by the system, as occurs in health, it presumably passes directly into the blood after a meal, causing a hyperglycæmia and consequent glycosuria. This naturally does not necessarily mean an over-formation of glucose. Von Noorden denies the over-production of sugar, but advances no conclusive evidence to support his contention.

2. Theory of Under-Consumption and Deficient Oxidation.—In health, the glucose of the blood is consumed mainly in the tissue-cells, particularly those of the muscles. Normally arterial blood contains more glucose than venous blood, which is evidence in favor of the above contention. If the tissue cells of diabetic individuals fail to consume glucose we would expect to find less difference between the percentage of glucose

in arterial and venous blood in diabetic than in healthy persons. Chauveau and Kaufmann estimated the sugar in the blood of the crural artery and vein in healthy and in diabetic dogs. They found the difference to be the same in both animals, and conclude that the capacity for consuming sugar is not lost in diabetes.

A healthy individual on a mixed diet gives out less carbonic acid than he receives of oxygen, the ratio being on an average 9 to 10. This is expressed by the fraction 0.9, and is called the respiratory quotient. If there were an under-consumption of glucose in the tissues we would expect the quotient to be much reduced. Voit and Leo have shown that there is no such reduction. Von Noorden, who is a vigorous supporter of the under-consumption theory, lays great stress on an observation of Weintraud and Laves, who found that the addition of small quantities of carbohydrates to the dietary of diabetics raises the respiratory quotient much less than in health. He considers that this is evidence that the glucose is not properly consumed in the tissues of diabetics. Another evidence in favor of under-consumption is that carbohydrates are not converted into fats as in health.

Lactic and glycuronic acids are considered by most physiologists to be intermediate products in the combustion of glucose in the system. Glycuronic acid, like glucose, is found in minute traces in normal urine. Mayer has found the glycuronic acid excretion considerably increased in diabetes, and as he has also found it increased in conditions of suboxidation he thinks he has demonstrated conclusively that diabetes is due to deficient oxidation in the tissues.

The evidence so far provided does not warrant us in asserting definitely that diabetes results from over-production and not under-consumption of glucose or *vice versa*. In the opinion of the writer, however, the evidence points much more strongly toward the view that the hyperglycæmia is due rather to under-consumption of glucose from a lowering of the powers of the tissues to oxidize carbohydrates, than to an over-production of glucose.

Pavy, it will be recalled, thinks that normally the ingested carbohydrates are converted by the intestinal villi largely into fat and into a proteid-carbohydrate, and that only a smaller quantity reaches the liver as glucose. In diabetes he thinks that this function of the villi is largely abolished; and that consequently a much larger quantity of sugar reaches the liver and general circulation, resulting in a hyperglycæmia.

Cantani holds that the sugar found in the diabetic individual is not ordinary glucose, but a paraglucose which the tissues are not capable of utilizing. Consequently it accumulates and a hyperglycæmia results. His view has not received substantiation.

Theory Based on the View that a Normal Glycolytic Ferment or Body is Lacking in Diabetes.—Lépine was the first to advance the hypothesis that diabetes resulted from the failure of the pancreas to produce a glycolytic ferment which was necessary to the liver in order for it to perform its glycogenic functions. The observations of Opie and Ssoblew on the relationship between disease of the islands of Langerhans of the pancreas and diabetes, and the recent important investigations of Otto Cohnheim and Rabel-Hirsch on the combustion of carbohydrates, have afforded evidence strongly supporting the view that the pancreas, pancreas and muscles,

or pancreas and liver, produce a glycolytic body which is necessary for carbohydrate metabolism, the absence of which leads to failure in the combustion of glucose and consequent hyperglycæmia. Their work has already been given in detail, and only the essential points will be recalled here to elucidate the theory under discussion. Opie showed that in diseases of the pancreas accompanied by diabetes, the islands of Langerhans were practically always diseased and presumably rendered functionless. He also found that in certain cases of diabetes the pancreas macroscopically appeared normal, but microscopically revealed degeneration of the islands of Langerhans as the only pathological change.

Cohnheim, in 1903, found that muscle juice of cats and dogs when added to a solution of glucose had no effect on the latter. When, however, the expressed juice of the pancreas was added to the mixture of muscle juice and glucose there was a rapid breaking-up of the glucose into alcohol and carbonic acid. He concluded that in normal animals a glycolytic ferment or body results from the interaction of substances produced by the pancreas and muscles, and that this is necessary for the combustion of glucose. Opie's observations on the pancreas suggest very strongly that the pancreatic part of the glycolytic body is produced by the islands of Langerhans, and Ssobolew claims to have shown that this is the case.

The work of these observers is extremely suggestive, and constitutes one of the most important contributions to our knowledge of the etiology of diabetes that has ever been made. It seems to afford an explanation for the development of diabetes after extirpation of the pancreas. Some observers claim to have found no disease of the islands of Langerhans in certain cases of diabetes. In these cases two possibilities present themselves. The islands may not be organically but functionally diseased. On the other hand the muscles may be at fault.

The evidence thus afforded seems to justify us in strongly suspecting that in health the pancreas and muscles (and possibly other tissue-cells) produce substances which, by their interaction on each other, yield a glycolytic body—call it a glycolytic ferment if we will—which is necessary for the proper combustion of the glucose in the body. This body may be necessary also for the normal glycogenic function of the liver to be carried on. Its absence would lead to an under-consumption of glucose with a resultant hyperglycæmia. It must not be forgotten that Cohnheim's results have not been confirmed by some of the workers who have repeated his experiments. Consequently, any explanation as to the etiology of diabetes based upon them is still in the hypothetical stage. If Cohnheim's work be correct it must necessarily add additional support to the view that the hyperglycæmia in diabetes is due rather to deficient consumption or lowered oxidation than to over-production of glucose.

One seems justified in predicting that in the future it will be shown that a much larger percentage of cases of diabetes is due to pancreatic disease than was formerly believed. The recent advances in our knowledge of the physiology and pathology of the gland seem to warrant this prediction.

It is quite probable that all cases of diabetes cannot definitely be attributed primarily to disordered metabolism—the cases of "pure" diabetes of Naunyn—or to pathological lesions in the pancreas. A com-

paratively small number are due primarily to functional or organic disease of the central nervous system, as noted in the consideration of the etiology.

Pathology.—The etiology and pathology of diabetes mellitus are so clearly related that it is almost impossible to discuss one without the other. In the section on etiology those morbid lesions which were believed to be the cause rather than the result of the diabetes have already been considered. Thus the organic lesions of the *nervous system*, *liver*, and *pancreas* which are so important in the etiology of diabetes, have been fully discussed. In order to prevent repetition, these will not be fully considered here. The morbid changes not already considered, and, particularly, those which are regarded as the result of the disease, will now be briefly considered.

The *blood* always shows a hyperglycæmia. The only exceptions to this rule are the cases of phloridzin diabetes and the other rare instances of so-called "renal" diabetes which have been described by Kemperer and Naunyn. In these cases there is a hypoglycæmia. The blood is often concentrated. The specific gravity may be increased or diminished, according to the water content. In cases with marked polyuria, in which the watery constituents of the blood are depleted, the red cells may be 6,000,000 per cmm. or more. The latter react differently from those of normal blood with certain aniline dyes. Bremer found that smears of diabetic blood, heated for six to ten minutes at 135° C. and immersed for one to two minutes in a 1 per cent. aqueous solution of congo-red, remained unstained, while smears of normal blood take the red stain. The red cells of diabetic blood also stain differently with eosin and methylene blue. The leukocytes are usually normal in number, or increased only in proportion to the concentration. The writer has observed a leukocytosis of from 18,000 to 25,000 in diabetic coma. The leukocytes contain glycogen. The alkalinity is reduced, particularly in coma. This is occasioned by the presence of β -oxybutyric and diacetic acids. Acetonæmia may occur. *Lipæmia* occasionally occurs. The fat may be detected in the form of numerous minute dancing granules in the serum in thick preparations of fresh blood. The separated serum has a decided milky appearance. Fraser, in 1903, reported a case in a diabetic with a fatal coma. The percentage of fat in the blood was 16.44 per cent. Fischer recorded a case with 18.12 per cent., the highest ever reported. According to Becquerel and Rodier, blood normally contains from 0.16 to 0.325 per cent. of fat. Exudates in the serous sacs may be turbid with fat. The lipæmia has been attributed to the over-ingestion of fats, to fatty degeneration of the viscera, and to deficient lipolysis. In Fraser's case, the appearance of the lipæmia was coincident with a marked reduction in the sugar of the blood, and he thinks that the fat may be derived from the glucose. The fat droplets take the characteristic stains with Sudan III and osmic acid.

No characteristic changes are to be found in the *gastro-intestinal tract*. Frerichs frequently found a thick layer of a fungus growth in the mucous membrane of the fauces and œsophagus. Occasionally the stomach has been found dilated. Swelling, redness, and ecchymoses of the gastric mucosa, have been noted. Tuberculous ulceration of the intestine may occur where there is pulmonary tuberculosis.

The *heart* may be hypertrophied, but this is rare. The myocardium is often pale and soft. In old-standing cases, advanced fatty degeneration of the muscle-fibers is common. Pericarditis and endocarditis rarely occur. Arteriosclerosis is rather common.

Of the *pulmonary* lesions, tuberculosis is probably the most common. The tissues of the diabetic seem to furnish a specially good medium for the growth of the tubercle bacillus. Acute bronchopneumonia and lobar pneumonia may occur, and either may terminate in gangrene. The writer has seen one case of bronchopneumonia terminate in abscess formation. Grohe, Kühne, and Ehrlich, have shown the cells of the pneumonic exudate to be rich in glycogen. A chronic non-tuberculous interstitial pneumonia has been described. So-called fatty emboli of the pulmonary arteries occur in coma, but are of no pathological significance.

The *liver* is usually somewhat enlarged, and fatty degeneration is common. The form of cirrhosis designated by Hanot as *cirrhose pigmentaire diabétique*, which is one of the lesions of hæmochromatosis in which diabetes may develop as a late manifestation, has already been described. Poverty of the liver in glycogen is a striking feature. The *pancreatic* lesions have been described. There are no changes in the gland that are regarded as secondary to the disease.

The *kidneys* are often enlarged. The most characteristic change is a hyaline degeneration of the epithelial cells of Henle's loop, described by Armanni and sometimes spoken of as the lesion of Armanni. The affected cells present a swollen, transparent appearance, as if transformed into large hyaline vesicles. The nuclei stain well and are pushed to the periphery. Cantanni and others have confirmed Armanni's observations. Ehrlich and Frerichs have described a glycogenic degeneration of the same cells as are involved in Armanni's lesion. The degeneration can be demonstrated macroscopically by treating the kidney section with Lugol's solution, the affected portion taking on a red color. Straus holds that the hyaline changes described by Armanni and the glycogenic changes described by Ehrlich and Frerichs, are really of the same nature. In some cases he has demonstrated the hyaline changes without finding glycogen present. In such cases, he thinks that the glycogen has been present at one time, but has disappeared before death, leaving only the hyaline changes. Ebstein has described a necrosis of the renal epithelial cells, similar to the coagulation necrosis of Weigert in other diseases. Interstitial and parenchymatous nephritis may occur, but there is no reason to believe that diabetes is the cause of the nephritis in these cases. A *cystitis* occasionally occurs. It has been attributed to irritation by the saccharine urine, but it is more likely due to bacterial infection.

Of the lesions of the *nervous system* not already described, Saundby states that congestion and œdema, and thickening of the membranes of the brain, may occur. Williamson, Sandmeyer, and Kalmus, have described a degeneration of the posterior columns of the cord similar to the sclerosis of these tracts in tabes dorsalis. Williamson states that the lesion is best seen with the naked eye, when the affected portions appear much paler than does the healthy white matter. These changes are attributed to the action of some toxic agent. The peripheral nerves, particularly those of the lower extremities, may be the seat of an interstitial inflammation, with secondary degeneration of the axis cylinders of

the nerve fibers. This *neuritis* may be the cause of definite clinical symptoms.

Symptoms.—Various writers have been disposed to recognize certain clinical types of the disease. Thus *acute* and *chronic* cases are described. The acute cases generally occur in children and young adults, the emaciation being marked and the course very rapid. The chronic cases usually occur in persons who develop the disease after the fortieth year, and in middle-aged and elderly obese individuals. The acute cases, however, may occur in the aged. Osler reports a man aged seventy-three years in whom the entire course of the disease was less than three weeks.

There are the *mild* and the *severe* cases. According to Naunyn, if the glucose disappears with the patient on a non-carbohydrate diet, the case belongs to the former type. If, on the other hand, he continues to excrete glucose, the case is a severe one, for it means that sugar is being produced from the body proteids. Further, we have the *fat* or lipogenous (*diabète gras*) and the *emaciated* (*diabète maigre*) cases. Lancereaux believed the latter were caused by lesions of the pancreas. *Exogenous* and *endogenous* cases have been described. The former embrace the cases in which there is some external exciting cause. The latter, according to Strümpell and others, include those in which there is no apparent external etiological factor, or any evident organic lesion, but in which the disease is thought to be due to some developmental abnormality. We have also the *neurotic* cases due to injuries or functional disorders of the nervous system. There is no fundamental difference in any of these cases, and no satisfactory classification, along the lines indicated, seems possible.

Although the disease is usually accompanied by a certain group of symptoms which especially characterize it, and which may be so abrupt in their onset that the patient can state the date of their appearance with considerable accuracy, yet these may for a long time remain in abeyance, and may even never become a prominent feature. Thus the polyuria, thirst, increased appetite, emaciation, and weakness, may not be sufficiently marked to attract the patient's attention. The first intimation of there being anything wrong may be a gradual failure in vision. An oculist is consulted who, finding a commencing or well-developed cataract or a retinitis, suspects diabetes, and orders an examination of the urine, which results in his suspicions being confirmed. On the other hand, the patient may consult the family physician for an obstinate general or localized pruritus as the first symptom, with the same results. Similarly, a furunculosis, a severe neuralgia, or impotence, may cause the patient to seek advice. Occasionally general weakness, nervousness, slight change in temperament, mental hebetude, and inability to apply himself to business, may antedate the characteristic symptoms. Too often, unfortunately, the cause of such symptoms is not discovered sufficiently early, and the disease gets a firm foothold and has seriously impaired the general health before it is finally recognized.

Polyuria is the symptom most frequently first complained of by the diabetic. In the acute cases, the patient asserts positively that the quantity of urine suddenly became greater, and that he is obliged to get up frequently at night to pass urine. The increase in the quantity of urine is referable to the hyperglycæmia. Owing to the increased quantity of glucose in the blood, the latter becomes hyperisotonic, and the fluids of the

tissues are absorbed into the circulation more rapidly than in the normal individual, and consequently more water is secreted by the kidneys. The amount of urine may reach 10 to 20 liters (5 to 10 quarts) daily in the severest cases, although it is rare to see cases in which more than 10 liters is voided in the twenty-four hours. The amount of urine in the majority of cases ranges between 2 and 5 liters. The quantity usually bears a direct relationship to the percentage of sugar excreted. In certain cases it is well to remember that there may be no increase in the urine even when glycosuria is present.

Thirst, or polydipsia, may be extreme, and may be complained of as early as, but more often very soon after, the polyuria. It is indirectly traceable to the hyperglycemia, and directly to the dessication of the tissues already described. It bears a definite relationship to the polyuria.

Increased appetite (bulimia or polyphagia) is a frequent symptom, particularly in the very acute cases. In the milder forms, and in the advanced stages of the severe type, this symptom may be wanting. There may even be loss of desire for food. Notwithstanding the enormous amount of food eaten, progressive emaciation is the rule, especially in the young individual. The increased appetite and the emaciation are largely dependent upon the same cause—the failure of the diabetic organism fully to utilize the carbohydrates of the food. The nutritive changes in diabetes are interesting and deserve some consideration. An individual doing light work requires about 40 calories for each kilo body-weight daily, although the recent work of Chittenden seems to indicate that this caloric requirement is too high. Thus a person of average weight would require food to yield 2,400 calories for his nutritive needs. Let us suppose this individual to be suffering from diabetes and to be taking a mixed diet including proteids, fats, and carbohydrates, in the following proportions with their caloric equivalents: 160 grams of albumin, yielding 656 calories; 110 grams of fat, yielding 1,023 calories; and 240 grams of carbohydrates, yielding 984 calories. This diet, therefore, would provide a total of 2,663 heat units, or 263 more than would be required by the individual were he perfectly healthy. Let us suppose, however, that he is excreting 140 grams of sugar daily. He would therefore lose each day nutritive material to the value of $140 \times 4.1 = 574$ calories. The food of this diabetic consequently would have the value of only $2,663 - 574 = 2,089$ calories. As the estimated nutritive need was 2,400, there was a daily deficit of $2,400 - 2,089 = 311$ calories. The body, therefore, in order to meet the requirements of energy and heat production, must have consumed of its own substance to the value of 311 calories. The tissues drawn on for fuel material to make up for this caloric deficit are, of course, the albuminous and fatty. By estimating the amount of nitrogen in the food and in the urine and feces, it is possible, accurately, to determine the exact proportion of body-fat and albumin consumed daily to make up for the caloric loss resulting from the failure of the organism to utilize all the ingested carbohydrates owing to a considerable quantity being eliminated in the urine as glucose. This consumption of his own body-fat and albumin necessarily occasions a progressive loss in weight, and the hypothetical case illustrates how the emaciation is brought about. The latter will continue unless the diet is so regulated as to prevent a loss of sugar in the urine. Von Noorden explains the polyphagia in the following way:

"The sufferer from this disease whose diet is not regulated by medical advice, swallows great quantities of food, including much carbohydrate. The 'stomach hunger' is momentarily stilled, but quickly returns, for 'tissue hunger' is not satisfied. The inordinate appetite of the diabetic disappears only when the useless carbohydrates are cut off and their place supplied by albumin and fat. When this is done the emaciation of the patient comes to a halt, with relief of the polyphagia."

The face is often of a deep red color. The skin of the entire body in the majority of cases is dry and harsh. This is due to the fact that the sweat, as is the case with nearly all the secretions, with the exception of the urine, is diminished in amount. The skin may be moist, however. In cases complicated by pulmonary tuberculosis, sweats may occur, and they have been known to alternate with polyuria. The nails are often brittle, and the hair thin and dry. There may be some irritability of temper. There is a strong tendency for the individual to become morose or even hypochondriacal. Some complain of extreme drowsiness during working hours. The temperature in uncomplicated cases is usually subnormal. The pulse is generally increased in frequency, with the pulse-tension above normal.

The mouth is dry, due to the thirst and to the diminished salivary secretion. The saliva is less alkaline than in health, and that collected from Steno's duct is usually acid in reaction. Frerichs, von Noorden, and Mosler, found the saliva almost without exception free from sugar. Frerichs demonstrated sugar in one out of nine cases. The tongue is usually dry and red, and often has a glossy appearance resembling that in psoriasis linguæ. The digestion, notwithstanding the enormous quantities of food taken, is, as a rule, good. Obstinate constipation is the rule. The eye-sight, owing to the ocular complications, is often defective. Pain in the lumbar region is often an annoying symptom even early in the disease. Cramps in the calves of the legs occasionally cause much discomfort. Owing to the lowered vitality of the tissues, and owing to the latter being richer in sugar than normally and consequently being a better nutritive medium for the growth of organisms, wounds heal less readily and are much more liable to become infected. In patients with secondary lesions of the cord or peripheral nerves of the lower extremities a sensation of a "giving away" of the knees may be complained of. This occasionally occurs, however, even without nervous manifestations.

Loss of sexual desire and power in men is common, and may be an early feature. It may reach the grade of actual impotence. Sexual power may return, according to Seegen, with improvement in the patient's other symptoms while under treatment. Occasionally increased sexual desire and power persist throughout the disease. In severe cases of diabetes in women the sexual desire is much impaired, but in mild cases in elderly women it is said to be often increased. Amenorrhœa is not uncommon, and may occur early in the disease.

The Urine.—The amount of urine has been considered under polyuria. It is usually extremely pale and clear. The quantity and pallor generally bear a direct relationship to the percentage of sugar present. Occasionally one sees diabetic urine of quite deep color. In these cases there is little or no polyuria. It often has a suggestive greenish tint, and may, when shaken, have a syrupy consistency. It has a sweet taste, and in severe cases

with threatening coma, may have a sweetish, fruity odor, owing to the presence of acetone. The specific gravity usually ranges between 1,025 and 1,045. A pale urine with a specific gravity above 1,025 should always lead one to suspect the presence of sugar. In rare instances diabetic urine with sugar demonstrable may have a specific gravity of 1,015 or even lower. A specific gravity above 1,050 is rare. Naunyn has seen a case with 1,060. The highest specific gravity recorded was in two cases reported by Bouchardat and Prout, in each of which it was 1,074. Very high specific gravities—1,070 or over—always suggest fraud.

The most characteristic feature is the presence of sugar and the diagnosis is largely dependent upon this. This is almost invariably grape-sugar (glucose, dextrose). Normal urine contains glucose in quantities not demonstrable by the ordinary tests. In rare instances levulosuria may occur either with glycosuria or alone. Authentic cases have been reported by Seegen, Külz, and May. Külz and Vogel have frequently noted pentosuria in human diabetes, and in experimental diabetes in animals, even after prolonged fasting, showing that the pentose originates in the animal body. The amount of sugar excreted varies considerably at different periods of the day. The period of minimum output is in the late night or early morning hours. According to Naunyn there are two periods of maximum output; one in the late morning hours, the other about six o'clock in the afternoon, occasionally lasting until midnight. The amount of sugar usually begins to increase about one and a half to two hours after a meal. The percentage of sugar should be determined from a sample of urine taken from the mixed twenty-four hour amount. Knowing the total amount of urine, it is then easy to calculate the total amount of sugar, in grams or grains, excreted daily. This is the only satisfactory way of following the progress from day to day or from week to week. Variations in the percentage of glucose excreted at different periods of the day are much less marked in the severe than in the mild cases, and in the former, the sugar of the night urine may exceed that of the day. In the latter, the variations are often quite marked and the urine of the early morning hours may be free from sugar. The percentage of glucose varies greatly. In the majority of cases it ranges about 3 per cent. In the severe cases it reaches 5 per cent. or over. It is very rare to meet with more than 8 or 9 per cent. although Naunyn reported a case with 11 per cent., and Higgins and Ogden a case of traumatic diabetes with 20 per cent. of glucose. The total output of sugar for the twenty-four hours may be only a few grams in the mild cases. In some cases the quantity of sugar may be enormous. It is not unusual to see cases with a daily excretion of 500 grams (15 oz.). Chareot reported a case with 1,100 grams (35 oz.), Lecorhé a case with 1,200 grams (38 oz.), and Dickinson, a case cited by Naunyn with the enormous output of 1,500 grams (48 oz.).

Many factors influence the sugar output. Diet is the most important one. Carbohydrates cause a marked increase, whereas a diet consisting exclusively of proteids and fat will cause the sugar to disappear in mild cases and will reduce it to a minimum in the severe cases. Acute febrile diseases and septic infections often cause a marked reduction. It is not unusual in diabetes with pulmonary tuberculosis accompanied by high fever, to see the sugar almost entirely disappear in the terminal stages.

The onset of coma manifestations with the appearance of β -oxybutyric acid in the urine is not infrequently attended by a marked reduction in the sugar excretion. The following are the most satisfactory tests for glucose:

Fehling's Test.—Two separate solutions are necessary unless one uses the Haines or Purdy modification. The copper solution contains 34.65 grams of pure crystallized copper sulphate to the liter of distilled water. The alkaline solution is prepared by dissolving 173 grams of Rochelle salt in 350 cc. water, adding 600 cc. of a caustic-soda solution of a specific gravity of 1.12, and diluting with distilled water to 1 liter. For the qualitative sugar test, equal quantities of the two solutions are mixed together, then boiled, and the suspected urine, after being freed from albumin, added a few drops at a time and then again heated. If glucose be present either the yellow hydroxide of copper or the red cuprous oxide will be precipitated. If reduction does not follow boiling, set aside for a while and a precipitation may occur on cooling, when only traces of sugar are present.

Although the Fehling's test requires considerable experience in order to secure absolute accuracy as a quantitative method of determining the amount of sugar, it is probably the least expensive and most accurate of the methods available for the general practitioner where mere approximate results are desired. This quantitative method is dependent upon the fact that 10 cc. of the copper sulphate solution is reduced by 0.05 grams of glucose. The determination is carried out as follows: 10 cc. each of the copper and alkaline solutions are mixed in a small flask and 30 cc. of water added. If the urine has a specific gravity approximately of 1,030 the urine is diluted five times, if over 1,030, ten times. A graduated burette is filled with the diluted urine. The Fehling's solution is boiled, and then the diluted urine is added at first about 1 cc. at a time and later in smaller quantity as the end reaction is approached. The solution is boiled after each addition of urine. The end reaction consists in the disappearance of the blue color immediately after boiling. The ability accurately to determine this point comes with experience. To determine whether the color has disappeared, allow the copper suboxide to settle a little below the meniscus formed by the surface of the liquid. If this layer is not blue on holding it on a level with the eye, the whole procedure is repeated adding 0.1 cc. less urine; if now, after the copper suboxide has settled, the supernatant liquid has a blue color, the titration is completed. Three or four estimations should be made in order to accurately determine the end reaction. Once the amount of urine required to reduce the 0.05 grams of copper sulphate in the 10 cc. of Fehling's copper solution has been ascertained, the calculation of the percentage is easy. Let us take an example for illustration and suppose that the urine has been diluted ten times, and that 8.5 cc. of diluted urine was necessary to complete the end reaction. We therefore know that the 8.5 cc. of urine used contain 0.05 grams of sugar and the percentage is therefore $(8.5 : 0.05 :: 100 : x) = 0.58$. This would be the percentage if the urine had not been diluted. Since the urine was diluted ten times the percentage of sugar in the undiluted urine would therefore be $0.58 \times 10 = 5.8$.

Trommer's test, in which a dilute copper sulphate solution and a solution of caustic soda or potash are used, while reliable in experienced

hands, is subject to too many fallacies to be used by the general practitioner. Excess of uric acid or creatinin will give a similar reaction.

Fermentation Test.—This is the most reliable single test we have. It is best carried out by using one of the fermentation tubes designed for bacteriological purposes, or one of the special tubes such as Einhorn's saccharimeter (made especially for urinary work) by which also the percentage of sugar can be roughly estimated. When yeast is added to diabetic urine and the mixture is kept at 22° to 28° C. for twenty-four hours, the sugar is decomposed and carbonic acid is given off. By measuring the gas given off from 10 cc. of diabetic urine (as is possible with Einhorn's saccharimeter), it is possible to determine the percentage of sugar. While this method is not absolutely accurate, for the purpose of following the progress from week to week it is sufficiently so for the general practitioner. As the yeast itself may cause a small evolution of gas, a control test with normal urine should always be made. The determination of the percentage of sugar by noting the reduction in the specific gravity after complete fermentation cannot be recommended.

Bismuth Test.—This is best performed with Nylander's modification of Almén's original solution. Nylander's solution is made by dissolving 4 grams of Rochelle salt in 100 parts of 10 per cent. caustic soda solution and adding 2 grams of bismuth subnitrate and digesting in a water-bath until as much of the salt is dissolved as possible. To 10 cc. of urine add 1 cc. of Nylander's solution and boil two or three minutes. If glucose be present the urine becomes yellowish, yellowish-brown and finally black from a deposition of metallic bismuth. A simple modification is to render 10 cc. of suspected urine alkaline with caustic soda and then add a small amount of bismuth subnitrate and then boil (Bötger's test). This on the whole is a delicate and reliable test. It shows 0.5 per mille of sugar. Combined glycuronic acid will cause a reduction and fallacies may result from the administration of chloral, salol, rhubarb, antipyrin, and turpentine.

Polariscope Test.—Glucose is dextro-rotatory, so that urine containing it will rotate the rays of polarized light to the right. By measuring the degree of rotation, the percentage of urine can be accurately determined when above 0.2 per cent. For hospital and laboratory purposes, it is the quickest and most satisfactory quantitative test. Half-shadow and circular-shadow polariscopes are made especially for estimating the quantity of sugar. Albumin should first be removed. β -oxybutyric acid is lævo-rotatory, and when present will neutralize some of the dextro-rotatory action of the glucose.

Phenylhydrazin Test.—This can be carried out by von Jaksch's simple method. To 8 to 10 cc. of urine in a test-tube add 2 knife-points of phenylhydrazin hydrochloride and 3 knife-points of sodium acetate, and if the salts do not dissolve on warming, add more water. Heat in a water-bath for one hour. Then cool by placing a test-tube in cold water. If sugar be present a yellow deposit of phenylglucosazone occurs which on microscopic examination is found to have a yellow color and to be arranged in sheaves and stars. Glycuronic acid and other substances yield similar crystals of an osazone. When any doubt arises, the crystals can be differentiated by determining their melting-points. Those yielded by glucose melt at 204° to 205° C.

While there are other tests for glucose, those above described are the ones which give the best results. Bremer showed that diabetic urine readily dissolved gentian violet powder, whereas normal urine fails to. He suggested this as a test. Unfortunately the urine in diabetes insipidus reacts in the same way.

Precautions to Observe in Performing the Sugar Tests.—It is a safe rule never to rely on one qualitative test alone. The most reliable single test is the fermentation test. If there is a rapid reduction of the copper sulphate in performing Fehling's test, one can be reasonably certain that the reducing agent is glucose. Where it is slow and slight, and, especially, if the precipitate be yellow rather than red, other reducing agents must be considered and eliminated. The other substances which reduce alkaline copper sulphate solutions are conjugated glycuronic acid sometimes eliminated after the taking of certain drugs, alkapton (homogentisic acid), lactose, excess of uric acid, and kreatinin. The conjugate glycuronic acid also reduces bismuth, but is differentiated from glucose by being lævo-rotatory as voided, becoming dextro-rotatory when the glycuronic acid is split off by boiling with an acid. It does not ferment. Alkaptonuric urine is recognized by being negative with the bismuth, fermentation, and polariscope tests. Its special feature is its darkening on exposure to the air and on the addition of an alkali. Lactose, which is very frequently eliminated in the urine in the early days of lactation, and when there is retention of the milk in the breasts either from obstruction of the milk-ducts or from sore nipples, reduces copper sulphate and bismuth, and is dextro-rotatory, but does not ferment. Although excesses of uric acid and kreatinin may cause slight reductions of copper sulphate, there should be no difficulty in differentiating these from glucose if one takes the precaution to use one or more of the other tests, with which they are negative.

It is a safe precaution to use at least both Fehling's and Nylander's bismuth solution as qualitative tests for sugar. The latter is a little more delicate and more reliable than the former. If a polariscope be available and the urine be found to be dextro-rotatory in action, there is little doubt about the reducing substance being glucose. When any doubt exists, the fermentation test, the most reliable of all, should be tried.

Other Urinary Ingredients in Diabetes.—Mayer has shown that *glycuronic acid*, like sugar, is present in normal urine in minute traces, and that it is increased in diabetes. It is regarded as one of the intermediary products of carbohydrate metabolism. It is recognized by the orein test. Rosin and Alfthan demonstrated that the benzoyl esters are also increased. These normally do not exceed 2 to 3 grams daily. Edsall has found as high as 12.5 and 13.8 grams respectively in three cases of diabetes.

Mayo Robson and Cammidge, have shown that in pancreatic disease glycerine is excreted in the urine. The *glycerine* results from the splitting up of the fat molecule in the areas of fat necrosis. Cammidge claims to have found it in one case of diabetes due to pancreatic disease. The details of the test cannot be given here. Considerable doubt has been expressed as to the value of this test and also as to whether the authors have properly interpreted their results.

The urine of diabetics before and during coma symptoms very frequently, if not always, contains β -oxybutyric acid and its derivative products,

diacetic acid and acetone. The tests for these substances may be briefly stated here.

It is possible, by a process too long to be described here, to isolate *β -oxybutyric acid* ($C_4H_5O_3$) from the urine in crystalline form. On being boiled with a mineral acid it is decomposed into α -crotonic acid, the crystals of which melt at 71 to 72° C., by which test it can be recognized. Its probable presence can be detected in two ways. Being a *laevo*-rotator, its presence may be assumed if, after completely fermenting the urine, the urine rotates the rays of polarized light to the left. For the same reason its presence may be suspected if the percentage of sugar is found to be considerably higher by the Fehling's than by the polariscope method. This is due to the fact that dextro-rotatory power of the glucose is partially neutralized by the *laevo*-rotary power of the acid.

Diacetic acid ($C_4H_6O_3$) is practically always present when the urine contains *β -oxybutyric acid*, but the reverse is not always the case. The molecule of *β -oxybutyric acid* by taking on an atom of oxygen splits up into diacetic acid and water. The former is now universally accepted to be the source of the latter. The urine must be fresh in testing for diacetic acid, for it readily breaks up into acetone and carbonic acid. It is recognized by Gerhardt's ferric chloride test. To 10 cc. of urine add a solution of ferric chloride until all the phosphates are precipitated as iron phosphate. Filter and continue to add ferric chloride to the filtrate. If diacetic acid be present, the urine now takes on a claret or Bordeaux-red color. Salicylic acid will give the same reaction. To differentiate them, boil a second portion of the urine for five minutes and follow the same procedure. If the Bordeaux-red color of the first test be due to diacetic acid, it fails to appear in the second, while it persists if due to salicylic acid, because the former is volatile and the latter is not. A third portion is treated with sulphuric acid and shaken with ether. The ether extract is decanted off and shaken with a very dilute watery solution of ferric chloride. If diacetic acid be present, the watery layer takes on a Bordeaux-red color which disappears on heating. It is very unstable and quickly becomes broken up into acetone and carbon dioxide. This instability renders it impossible to quantitatively determine the amount of diacetic acid in the urine. The diacetic acid and acetone are estimated together and recorded in terms of total acetone.

Acetone (C_3H_6O), when present in large quantities, may give the urine a fruity odor. It may be recognized by Legal's sodium-nitroprusside test. To 10 cc. of urine add a few drops of a fresh solution of sodium nitroprusside. Then add caustic potash or soda solution, and, if acetone be present, the urine assumes a ruby-red color. Creatinin gives the same color, but if glacial acetic acid be now added the color becomes carmine or purplish-red in the presence of acetone, but yellow and gradually green or blue in the presence of creatinin. This test is not so delicate as Lieben's iodoform test. Distil the urine and treat the distillate with caustic potash, and then add Lugol's solution. If acetone be present, the distillate becomes yellowish-white, owing to the formation of iodoform, which is recognized by its odor and by hexagonal or stellar crystals on microscopic examination. A very large percentage of diabetic urines will give a positive reaction with this test. For mere traces of acetone it is the most delicate of the various tests. Of the three substances just con-

sidered it is the one most frequently found. There is no relationship between the quantity of these "acetone bodies," as the three are often called, and the amount of sugar excreted.

The *nitrogen* output is greatly increased, chiefly in the form of urea. This is due largely to the greater amount of proteids ingested, but also in part to increased destruction of the body proteids in the more severe cases. Pettenkofer and Voit have shown that, even when fasting, a diabetic patient excreted about 8 per cent. more urea than a healthy person. Leo has shown that the addition of carbohydrates to the diet of a diabetic will occasionally diminish nitrogenous metabolism.

An interesting feature is the extraordinary increase in the *ammonia* output in the severe cases, particularly when coma supervenes. According to Neubauer, the average amount of ammonia excreted in the urine by a normal individual on a mixed diet is about 0.7 grams daily. Part of the ammonia which should go to form urea is utilized in neutralizing the acids producing the acid intoxication. Naunyn reports having found an excretion of 5.8 grams of ammonia in a child weighing 48 pounds, and states that a daily excretion of 6 to 7 grams is not unusual in adult diabetics. Although this amount is not often exceeded, Stadelmann records a case with an elimination of 11 grams. The amount of ammonia excretion can be taken as a safe measure of the grade of acid intoxication in diabetes.

The *uric acid* excretion is usually increased, as has been shown by Naunyn, Riess, and others. Gaethgens, in a diabetic with fever, found the uric-acid excretion was 2.2 grams in the twenty-four hours. The increase is explained by the excessive proteids taken. It is very common to see diabetic urines with uric acid sediments. This precipitation is probably in part due to the diminished power of diabetic urine to retain uric acid in solution. Bischofswerder has shown that the total *alloxuric bodies* are also increased. Senator found the creatinin increased up to 2 grams daily. This is referable to the increased ingestion of meat and to the increased destruction of the muscular tissues of the body.

Oxaluria often occurs, with an actual increase in the excretion of calcium oxalate. Teubauum has shown that the lime-salts are markedly increased in severe cases of diabetes, but not in the mild. The *sodium chloride* is increased. The *sulphates* and *phosphates* are in excess, owing to the increased destruction of ingested and body proteid, with oxidation of the sulphur and phosphorus of the proteid molecule. A form of "phosphatic diabetes" has been described by Tessier, Ralfe, and others, due to an excessive excretion of calcium phosphate. There is nervous irritability, deranged digestion, emaciation, and pain in the back. In severe cases there may be polyuria, and the symptoms may simulate diabetes. The affection has really nothing to do with true diabetes, although it is said that traces of sugar have been found in some cases or have subsequently developed.

Albuminuria is absent in the majority of cases of diabetes when they are first admitted to a general hospital. In private practice, where a larger proportion of mild diabetes in elderly persons is met with, it is more common. Five groups of cases of albuminuria may be recognized: (1) Cases of severe diabetes of considerable duration, with traces of albumin, but no other evidence of actual nephritis. (2) Those in dia-

betics of advanced age, with indications of arterial changes. (3) Those in which, in addition to albuminuria, there are evidences of chronic nephritis, such as œdema, headaches, albuminuric retinitis, and cardiovascular changes. (4) Cases of severe diabetes complicated by diabetic coma. When coma symptoms have definitely manifested themselves, albuminuria is practically always present. (5) Cases in which the albuminuria is due to a cystitis, or a balanitis in the male and vulvitis in the female. Naunyn and others state that diabetes mellitus occasionally passes over into a true nephritis, with disappearance of the glycosuria.

Casts are rare in diabetic urine except in those cases complicated by actual nephritis. There is one striking exception, however. Külz first pointed out that diabetic coma is accompanied by an abundant deposit of casts. A urine previously free from them and quite clear may suddenly become turbid, even on voiding, owing to the enormous number of casts present. In a very short time these settle to the very bottom of the glass as a grayish-white sediment. When pipetted off and examined microscopically, the field is found to be crowded with rather short hyaline and granular casts. The albuminuria and cylindruria of diabetic coma are probably evidences of a toxic nephritis. In cases of cystitis, balanitis, and vulvitis, pus-cells will be found in the urinary sediment.

Diabetic urine, on standing, soon becomes turbid, owing to the growth of yeast-cells. This fact is of practical importance, as it indicates that suspected urine should be examined qualitatively and quantitatively as soon as possible after being voided, particularly in warm weather. The yeast causes fermentation of the sugar, and where the glycosuria is slight, it may cause a complete disappearance of the glucose, and in all cases will cause a reduction in the percentage of sugar on quantitative determination. The presence of yeast-cells in a urinary sediment should always arouse a suspicion of the existence of glucose. In balanitis in the male and vulvitis in the female, resulting from the constant irritation of the saccharine urine, there is often a fungus growth in the inflamed mucous surfaces, and fungus spores and mycelia may consequently be washed away in the urine during the act of voiding. These may be recognized in the urine on microscopic examination.

Occasionally yeast-cells and fungi develop in the bladder and set up fermentation processes, with the evolution of gas, producing *pneumaturia*. This is a rare condition. Leube found that diabetic urine contains a substance which gives all the reactions of *glycogen*. *Lipuria* has been described, the fat occurring in the form of a fine emulsion.

Complications.—1. **The Skin.**—*Boils* and *carbuncles* are very common, so much so that when they exist one immediately thinks of diabetes as a cause. Their frequency is due to the susceptibility of the tissues of the diabetic to infection. Boils are more common in the milder forms of the disease and in stout diabetics. Seegen says he has never seen boils in an advanced stage of the disease. The commonest seats are the neck, back, and buttocks. Cultures usually show staphylococci, and the *Staphylococcus aureus* or *albus* may occur in pure culture. Carbuncles are less common but more serious. They are more likely to occur in the severe cases. The commonest situations are the back of the neck and between the shoulders. With the surrounding cellulitis the area involved may reach 20 cm. (8 in.) or more. They may precipitate an attack of coma.

Owing to the irritation of the genitals by the saccharine urine, and to the growth of fungi (hyphomycetes) in the superficial layers of the skin, inflammation of the prepuce and glans in the male, and vulvitis in the female, may occur. This may be attended by intolerable *pruritus pudendi*, particularly in women, in whom local boils or phlegmons of the genitals may develop. The *general pruritus* of diabetes is due in all probability to irritation of the sensory nerves by the sugar in the blood, just as *pruritus* in jaundice and uræmia is due to circulating toxins. *Urticaria*, *purpura simplex*, *purpura hemorrhagica*, *dermatitis herpetiformis*, *gangræna diabetica bullosa serpiginosa* (Koposi) may occur. *Edema* of the feet, even without evident renal or cardiac affections, is not uncommon in advanced cachectic cases. A curious mottled cyanosis of the extremities is sometimes observed. In rare instances, the skin may be bronzed, constituting the so-called *diabète bronzé* cases. The pigmentation is a symptom of the disease known as hæmochromatosis, in which glycosuria sometimes occurs in the late stages when the interstitial pancreatitis becomes marked. *Herpes zoster* and *perforating ulcer* of the foot occasionally occur, and are expressions of a diabetic neuritis. A *paronychia diabetica* may occur. This may result in the loss of the nails. Williamson has observed three cases with bulbous fingers, due apparently to vasomotor changes.

Spontaneous diabetic gangrene occurs usually in diabetics after fifty. The glycosuria is usually of a mild grade. It is commonest in the lower extremities, and generally begins with a bluish discoloration and then a blackening of the skin of the big or little toe. It is of a moist type and may subside, but usually extends gradually to involve the whole foot or leg until stopped by amputation. It may start in the heel. William Hunt analyzed 64 cases. In 50 the distribution was as follows: feet and legs, 37; thigh and buttock, 2; nape of the neck, 2; external genitals, 1; lungs, 3; fingers, 3; back, 1; eyes, 1. The artery supplying the affected area shows arteriosclerosis in the vast majority of cases. In many instances it is thrombosed, and Naunyn states that he has never failed to find obliteration of the pulse in the early stages of the complication. Phlebitis, particularly of the veins of the leg, occasionally occurs. It was present in 1 case in the Johns Hopkins Hospital series.

Xanthoma diabeticorum occurs as a very rare complication. Up to 1892, Morris could find only 21 cases reported. The lesions consist of small nodules about the size of a pea, and having a yellowish or yellowish-red color. They are slightly sensitive and occur mainly on the buttocks, forearms, and knees. The eyelids are much less likely to be involved than in the xanthoma multiplex accompanying chronic jaundice. The xanthomata appear rapidly and disappear quickly with relief of the glycosuria by diabetic treatment. They may recur several times.

2. Gastro-Intestinal.—An aphthous stomatitis due to the oïdium albicans occasionally occurs. At autopsy the pharynx and œsophagus often show a diffuse growth of this fungus. Gingivitis with pyorrhœa alveolaris frequently develops. The teeth decay rapidly and tend to loosen and fall out. The latter is probably due to a trophoneurosis. Gastrectasia occasionally results from the enormous quantities of food and liquids taken. There may be actual gastric catarrh. Although moderate constipation is the rule, one occasionally meets with a case with obstinate diarrhœa. This

is referable to an intestinal catarrh. Steatorrhœa, or fatty stools, may occur in pancreatic diabetes. Here fat digestion is interfered with, owing to changes in the pancreatic secretion, and the stools are of a pulpy consistence, of a dirty, dark-gray color, and of a greasy appearance. In these cases the movements are often very bulky, and at the end of defecation as much as a tablespoonful of almost pure fat may be passed. In a patient seen with A. D. Atkinson, of Baltimore, the autopsy revealed the presence of a large pancreatic calculus. Microscopically, large oil-globules and abundance of fatty acid and soap crystals are seen.

3. Pulmonary.—One of the commonest is *pulmonary tuberculosis*. Griesinger analyzed 250 cases of diabetes, and found pulmonary tuberculosis present in 42 per cent., and to be the cause of death in 39 per cent. In 50 autopsies, Frerichs found the lungs tuberculous in 25. In 149 of Naunyn's "pure" diabetes cases, it was present in 25, or 17 per cent., while in 113 cases, due to evident organic disease, there were 8, or 7 per cent. With the progress of the tuberculous process the glycosuria often diminishes, or may entirely disappear.

Death may result from acute pneumonia, either lobar or lobular. A chronic interstitial pneumonia may occur. The pneumonia may be complicated by abscess of the lung. In 1 of the Johns Hopkins series there were multiple abscesses in the pneumonic area. Gangrene of the lung is not very uncommon. Naunyn saw 12 cases, all of which terminated fatally with one exception. He describes three forms—an acute, a sub-acute or chronic, and a form with numerous gangrenous foci complicating a chronic pneumonic process, with fibrous induration.

4. Renal.—These have been sufficiently dealt with in the accounts of the pathology and of the urine.

5. Nervous System.—Here only the nervous features directly referable to the diabetes will be considered. It is of interest that glucose has been found in the fluid obtained by lumbar puncture.

(a) *Peripheral Neuritis.*—This is the commonest nerve complication. The numbness, tingling, cramps, and neuralgias, are probably expressions of a mild neuritis. Sciatica is not uncommon, and other peripheral nerves, such as the inferior dental, may be affected. The neuritis may be multiple. Thus both ulnar nerves may be involved, causing muscular paralysis and anæsthesia of the skin. As expressions of the neuritis, must be mentioned *falling out of the nails, glossy fingers, herpes zoster, and perforating ulcer of the foot*. The perforating ulcer closely resembles that of tabes. Williamson met 4 out of 140 cases. It occurs nearly always in men, and in apparently mild cases. The sole of the foot, in the region of the metatarsophalangeal joint, is the commonest seat. The bone may be exposed or the joint opened. A corn may precede the ulcer. Attempts to remove the corn lead to infection, and the ulcer proceeds. On the other hand, trophic changes, due to the neuritis, constitute the chief etiological factor, and the ulcer may commence with superficial death of the skin. The ulceration is often painless. As the knee-jerks are often absent, the lesion may be mistaken for the perforating ulcer of tabes unless the urine is examined.

A so-called *diabetic tabes*, resulting from a polyneuritis, has been described. This pseudotabes closely resembles true tabes dorsalis, and was first described by Fischer, in 1886. It is characterized by lightning

pains in the legs, loss of knee-jerks, and loss of power of the extensors of the feet. There is a characteristic *steppage* gait similar to that seen in arsenical, alcoholic, and in other forms of neuritic paralysis. A typical Argyll-Robertson pupil is rarely, if ever, present, although Charcot states that there may be atrophy of the optic nerve.

(b) A *diabetic paraplegia*, probably due to a peripheral neuritis, with paralysis of the arms and legs, has been described.

(c) Degeneration of the posterior columns has been described by Williamson, Sandmeyer, and Kalmus. This lesion has been considered in the section on pathology.

(d) *Hemiplegia* occasionally occurs. One would naturally expect to find some gross lesion to account for the paralysis, but cases have been reported in which careful search has failed to find any evidences of hemorrhage or thrombosis. The hemiplegia in these cases has been attributed to toxic causes, similar to the cases of hemiplegia in uræmia without manifest brain lesions. Careful microscopic examination of the brain is necessary in these cases before stating that there is no organic lesion, and a thrombosed vessel may explain the complication.

In this connection the condition of the *tendon reflexes* may be considered. The knee-jerks are often absent, as first pointed out by Bouchard. Statistics differ as to the frequency with which the knee-jerks disappear. Grube found them absent in only 13.5 per cent. of his cases, whereas Williamson found them absent in 50 per cent of his series. Their disappearance is probably dependent on a peripheral neuritis, or changes in the posterior columns of the cord. The Achilles-reflex may disappear before the patellar, as in locomotor ataxia. The superficial reflexes—plantar, abdominal, and epigastric—are present in practically all cases. A patellar reflex may return after being lost. The condition of the reflexes bears no definite relationship to the prognosis, although the knee-jerks are more likely to be found absent in hospital than in private practice, the former cases being usually more severe than the latter.

(e) *Mental Complications*.—In addition to the psychical symptoms already described, a group of mental symptoms is occasionally met with closely resembling *general paresis*. Laudenheimer reviewed the relationship between diabetes and general paresis, and concludes that diabetes is not actually the cause of the latter. The mental symptom-complex is often improved under anti-diabetic treatment. It has already been pointed out that actual general paresis is quite frequently the cause of glycosuria.

6. Special Senses.—Of the ocular complications, *cataract* is the commonest. Frerichs observed it in 19 cases out of 400 diabetics; Williamson, in 9 out of 100; and Seegen, in 4 per cent. of his cases. It occurs in the young as well as in the old. It is usually bilateral, and, in the young, of the soft variety, but in old diabetic patients it is indistinguishable from the non-diabetic variety. There is no satisfactory explanation of its cause. The view that it is due to abstraction of water is no longer generally supported. Diabetic retinitis occurs, but is not so common as albuminuric retinitis. Williamson found it in 7 cases out of a 100 diabetics, but in some of these, renal disease could not be excluded as a cause. It was first described by Jæger, in 1856. Hirschberg describes three types—a retinitis hemorrhagica diabetica, a retinitis centralis punctata, and a

combined form. Rarely a *diabetic iritis* with hypopyon occurs. Diabetic amblyopia, due to a central scotoma, and *optic neuritis*, are rare complications. De Schweinitz says that *premature presbyopia*, with failure to accommodate, is a common and often an early symptom. Sudden amaurosis similar to that in uræmia may occur. The vitreous may contain masses of cholesterol crystals. Such a case has recently come under the writer's observation.

Ear complications are not common. Furuncles in the external auditory meatus, and acute otitis media occasionally occur.

7. Sexual Complications.—Most of the sexual symptoms have already been dealt with, but the relationship of diabetes to pregnancy will be considered here. Matthews Duncan, Kleinwächter, and Herman, have specially considered this subject. When diabetes develops during the child-bearing period, amenorrhœa usually results, and it is said that atrophy of the uterus may occur. Conception is rare. According to Gaudard, 33 per cent. of pregnant diabetic women abort. Herman states that premature delivery, due to intra-uterine death of the fœtus, has occurred in about two-thirds of the published cases of pregnancy with diabetes. A diabetic mother may bear a healthy child, however, and has never been known to bear a diabetic one. Usually the diabetes becomes aggravated after delivery. Pregnancy may go on to full term in certain instances with marked amelioration or complete disappearance of the diabetic features. Herman favors early delivery, for the reason that the chances are two to one that the child will die *in utero*, and that the earlier the pregnancy ends the more likely are the diabetic symptoms to ameliorate in the mother.

8. Diabetic Coma.—This is the most important and most serious of the complications of diabetes. It was first described by Kussmaul, in 1874. Three types of coma occur:

(a) *Typical dyspnœic coma*, or Kussmaul's "air-hunger" type. This is the form that Kussmaul described, and is by far the most frequent of the three. He observed three cases of this type at his Freiburg clinic in the year 1874. As premonitory symptoms there may be lassitude, headache, epigastric pain, and occasional vomiting. The patient becomes restless and excited, and tosses about in bed. His speech becomes thick and eventually incoherent. He grows gradually duller, and eventually passes into deep coma. The pulse becomes small in volume, of low tension, and frequent, often reaching to between 120 and 140 per minute. A characteristic form of dyspnœa develops. It is inspiratory at first, but later expiration is also involved. When fully developed the respirations are full and voluminous; they are loud and can be heard a considerable distance, although they are not stertorous as in apoplexy; they are quite regular and are usually not increased in frequency. The volume of the chest is greatly increased with each inspiration, and it is this apparent demand of the system for air that led Kussmaul to designate the phenomenon as "air-hunger." The temperature is usually subnormal. There may be some cyanosis. The breath often has a fruity odor (owing to the exhalation of acetone), which may pervade the whole room. The urine may also have an acetone odor. Traces of albumin and enormous numbers of short hyaline and granular casts occur in the urine just before and during the coma. Death almost invariably results, and occurs within

forty-eight to seventy-two hours after the onset of the coma. Frerichs and others recognize also the two following forms:

(b) *The So-called Alcoholic Form.*—With headache and symptoms suggesting alcoholic intoxication; the speech becomes thick, the pulse rapid, and, without dyspnoea, coma supervenes and the patient soon dies.

(c) *The Diabetic Collapse.*—The patient suddenly begins to suffer from drowsiness and great weakness. The extremities become cold; the hands, feet, and face, become livid; the pulse is small, thread-like, and 120 to 130 to the minute. The respirations are slightly quickened, but are shallow and not dyspnoeic in character. Drowsiness develops, coma supervenes, and the patient dies in ten to twenty hours. There is no acetone odor to the breath nor acetone or diacetic acid in the urine. The collapse is believed to be due to cardiac failure, probably induced by myocardial changes.

Anomalous forms of coma occur due to renal disease, cerebral tumor, meningitis, and apoplexy. The coma in these cases is due to the accompanying disease, and not to the diabetes.

The true diabetic coma of Kussmaul, or the "air-hunger" type, is by all means the most frequent and most important, and the following considerations mainly concern this form. A large percentage of deaths in diabetes are due to coma, and it is almost invariably the cause in children. An idea of its frequency can be gathered from the following statistics: Of Naunyn's 44 fatal cases, 19 died in coma, 12 of which were of the dyspnoeic type. Frerichs reported 150 deaths from coma out of a total of 250 fatal cases; Taylor, 26 out of 43; Mackenzie, 19 out of 87; and Williamson, 28 out of 40.

Certain factors tend to predispose to the development of coma. Among these are constipation, excessive fatigue, the onset of various complications such as carbuncle and pneumonia, subjection to an operation, and sudden changes in diet.

The complication is universally recognized now to be a manifestation of an acid auto-intoxication due to the abnormal circulation of β -oxybutyric acid in the blood. Previous to the establishment of this view, diabetic coma had been attributed successively to the action of acetone and diacetic acid. Both these substances, however, were shown to be innocuous when injected into animals. The chief developments in our knowledge of the actual cause of coma took place between 1880 and 1885. In 1880, Hallerworden found that the urine of many diabetics showed a remarkable increase in the ammonia output. As the urine in these cases was always markedly acid he thought there must also be a marked increase in the excretion of certain inorganic acids, eliminated as ammonium salts. Stadelmann, in 1883, proved the correctness of this hypothesis. For a series of successive days, he estimated the total mineral acids and mineral bases, including the ammonia, in the urine of a healthy man and a diabetic, and compared them in terms of sodium. On comparison he found that in the normal individual the sum of the acid equivalents slightly exceeded that of the bases. In the diabetic, on the other hand, the bases were far in excess of the acids. He concluded, therefore, that in order to satisfy the great excess in bases, an inorganic acid must be excreted in large quantities. He succeeded in isolating an acid which proved to be α -crotonic acid ($C_4H_6O_2$) but it was shown later that

this acid was not excreted as such in the urine, but that it was a decomposition product of another acid which Minkowski isolated in pure form in 1884, and which he characterized as β -oxybutyric ($C_4H_8O_3$). Independently, and practically simultaneously, Külz isolated the same acid from the urine of a diabetic patient.

Stadelmann is given, and deserves, the credit for first suggesting that diabetic coma is due to an acid intoxication. The diabetic patient who was the subject of his first research died of typical dyspnoëic coma. Walter had shown that when mineral acids were injected into animals, marked dyspnoea, frequent pulse, collapse, and death ensue, the symptoms being very similar to those in diabetic coma. As Stadelmann had found an excess of acid in the blood of the patient, and was familiar with Walter's experimental work, he concluded that diabetic coma resulted from an acid intoxication, and recommended that the coma symptoms should be treated by the administration of large doses of alkalis. His theory and suggestions as to practical treatment have been borne out by subsequent investigations.

Without qualification we can, at present, say that the acid intoxication of diabetic coma, or "acidosis" as Naunyn calls it, is due to the action of β -oxybutyric acid. By its action on the respiratory centre it causes the characteristic dyspnoea; and from its effect on the brain in general, coma supervenes. The β -oxybutyric acid is eliminated in the urine not as such, but in combination with the bases, chiefly as sodium oxybutyrate. In severe cases the output is enormous, reaching to between 100 and 200 grams daily, and in a case reported by Külz, to 225 grams. For a considerable time the available bases of the tissues (sodium, potassium, etc.,) are sufficient to neutralize the acid; but when it is excreted for long periods these become used up, and then ammonia, derived from proteid destruction, is called on for purposes of neutralization. This accounts for the enormous output of ammonia, reaching to seven or eight grams in cases of threatened coma. We have already shown that diacetic acid and acetone are derivative products of β -oxybutyric acid, and it is, therefore, not surprising that we also find these substances in the urine. The acetone excretion in the urine may reach 10 grams or more daily. That an acetonæmia exists is indicated by the acetone odor of the breath in coma cases. The presence of diacetic acid in the urine in the vast percentage of cases means that β -oxybutyric is also present. Owing to the difficulty in performing the tests for β -oxybutyric acid, clinically, we rely mainly on the ferric-chloride test for diacetic acid to indicate that an acid auto-intoxication exists. Acetone and diacetic acid are formed not alone from β -oxybutyric acid. This is indicated by their sometimes being present in the urine without the latter. It is now generally recognized that acetone is practically always formed from fat.

The presence of β -oxybutyric acid or diacetic acid in the urine should always serve as a danger-signal of approaching coma. There are exceptions to this rule, however, for one occasionally meets with cases in which a marked diacetic-acid reaction persists for months. Naunyn refers to a case in which there was an excretion of 100 grams of β -oxybutyric acid lasting for months, and of another diabetic in whom it had been detected for years. These are exceptional cases, however.

The source of the β -oxybutyric acid in the system has now been definitely settled. Until recently it had been attributed by nearly all investigators to destruction of the body-proteids. Some comparatively recent researches of Geelmuyden, Magnus-Levy, and others, have shown conclusively that the β -oxybutyric acid and its two derivatives are produced as a result of the incomplete combustion of the fats of the body, as well as of those of the food. The latter suggests that it may also result from synthesis in the muscles or glands. It is particularly in the cases with this acid intoxication that we have the best proof that fat metabolism is also disturbed in this disease. Naunyn formerly supported the view that β -oxybutyric acid is derived largely, if not entirely, from proteid. In the second edition of his work on diabetes, which appeared in 1906, he acknowledges that fat is undoubtedly a source of the "acetone bodies," as β -oxybutyric acid and its two derivatives are termed. One gets the impression, however, that he has not altogether abandoned the view that proteids may also be a source.

The relative amounts of acetone, diacetic acid and β -oxybutyric acid excreted may vary markedly in different stages of the disease. The first to appear is acetone, then diacetic acid, and lastly β -oxybutyric acid. In advanced stages of the disease, β -oxybutyric acid may be excreted in large amounts, acetone having practically disappeared from the urine. These changes are due to the gradual diminution of the powers of oxidation in the body. When it is possible to improve the body metabolism the acetone bodies disappear in the inverse order in which they make their appearance.

As a general rule, the addition of moderate amounts of carbohydrates to the diet causes a diminution in the excretion of acetone, as well as of the β -oxybutyric acid when it is present; their withdrawal causes an increase. While this is the rule in the mild cases, in the severest there are often exceptions. It seems to be quite certain that, when the capacity for oxidation in the body is not too much lowered, the presence of moderate amounts of carbohydrates in the food aids in the oxidation process and protects from destruction the fat which is believed to be the main source of the acetone bodies. The feeding of fats, however, seems to be a frequent cause for an increase in these bodies, as has been shown by Schwartz and others. Joslin has demonstrated that the extent of acetone excretion depends on the capability of the fat for absorption, hence on the character of the fat employed. It can readily be seen how important these considerations are and how directly they bear on the regulation of the diet when there are evidences of an acid intoxication in this disease.

With the development of coma manifestations and the appearance of β -oxybutyric acid in the urine, the sugar excretion often markedly diminishes, and the percentage of acid, which rarely reaches beyond 0.5 to 1 per cent., may exceed that of the sugar.

Saunders and Hamilton found the pulmonary capillaries plugged with fat in certain cases of diabetes with coma. They advanced the view that diabetic coma was due to fat-embolism of the pulmonary arteries. This view is no longer held.

Course and Prognosis.—In children and very young individuals, diabetes runs a very rapid course, and, almost invariably, death is caused by coma. Cases are recorded by Benson, Becker, Bohn, and Wallach, in

young individuals in which the disease ran its entire course to a fatal termination within five weeks. Generally speaking, the later in life the symptoms first manifest themselves, the better the prognosis is. The majority of cases after middle life run a chronic course, and it is not very uncommon to see stout, elderly individuals in whom the disease has lasted ten to fifteen years. Cases without hereditary influences are the most favorable. Once the disease is well established, it is seldom, if ever, that a permanent cure is effected. Occasionally, however, one sees a glycosuria persisting for months or years in a very neurotic individual eventually entirely disappear. Naunyn cites cases of acute or subacute diabetes resulting from head-traumas in which there has been a permanent cure. The thought naturally arises, are these cases true diabetes, or are they instances of traumatic glycosuria? It is always well to determine the power of the individual to warehouse carbohydrates. If an individual on a non-carbohydrate diet excretes no sugar, the case may be considered a mild one. If, on the other hand, sugar is excreted, it means that it is being manufactured from the body-proteids, and the case is a severe one. The tolerance of a diabetic to carbohydrates is determined by ascertaining the number of grams of starch that can be added to the diet without sugar appearing in the urine. The presence of β -oxybutyric acid and diacetic acid in the urine is in the majority of instances of serious import, as they indicate the possibility of approaching coma. Once coma is well established, a fatal termination almost invariably results no matter how active the treatment may be.

Diagnosis.—There is usually no difficulty in arriving at a diagnosis if the precaution be taken to use two or three urinary tests, including fermentation, in any doubtful case. It is sometimes difficult to determine whether one is dealing with a true diabetes or a symptomatic glycosuria. Time is the main factor in arriving at a decision in these instances. The presence of conjugate glycuronic-acid compounds, homogentisic acid (alkaptonuria), lactose, excess of uric acid, or creatinin, may cause error in inexperienced hands. The differential tests have been considered in the section on the urine. In a few of the cases of alkaptonuria the condition has been mistaken at first for diabetes. This was true in the case reported by the writer. The mistake is due to the fact that the homogentisic acid which is eliminated in the urine reduced alkaline copper sulphate solutions. The characteristic which the urine possesses of darkening on standing or on the addition of an alkali should arouse one's suspicions. Alkaptonuric urine, further, is negative with the bismuth, phenylhydrazine, fermentation, and polariscope tests. Bremer's blood-test may be of some value when a patient is seen for the first time with suspected coma symptoms and no urine is available.

Deception may be practiced by the patient. Osler cites a case under his care of a young girl who had a urine with a specific gravity of 1065, and in which the sugar-reactions proved to be those of cane-sugar. The literature records one case in which a woman, after detection, bought cane-sugar and introduced it into her bladder!

Pentosuria, although only nineteen cases have been recorded, is probably more common than is generally supposed. Some of the cases have been mistaken for diabetes. Salkowski and Jastrowitz reported the first case in 1892. The urine contained a copper reducing substance which was

optically inactive, did not ferment, and which from its osazone they identified as pentose. C. Janeway has recently reported two cases in brothers and states that there is a family predisposition to the disease. He describes three forms: (1) the alimentary pentosuria, due to the ingestion of large amounts of vegetables or fruits containing pentosanes; (2) rare cases occurring in severe diabetes in which the inability to burn carbohydrates extends to the pentoses; (3) chronic pentosuria occurring without reference to the pentoses of the food. The sugar excreted in this form is the optically inactive *r*-arabinose. Pentosuria is recognized as follows: Fehling's solution is reduced in an atypical way, the color remaining unchanged for a minute or so after boiling and then turning suddenly a green yellow or muddy orange color throughout. It gives the phenylhydrazine test, but is optically inactive and does not ferment. If doubt still remains the oricin test must be performed, in which the characteristic absorption bands of pentose are examined for with the spectroscope.

Treatment.—Prophylactic measures should be taken in families in which there is a predisposition toward diabetes. Often there is also a tendency to obesity in these families. It is advisable to determine the ability of its individual members to warehouse carbohydrates. If glycosuria results from administering 100 grams of glucose on an empty stomach, it may be concluded that the assimilation for carbohydrates is lowered, for a normal person can take from 180 to 250 grams of glucose without sugar appearing in the urine. By restricting the carbohydrates in the members whose assimilation limit is shown to be lowered, von Noorden thinks that the possible development of diabetes in these individuals may be warded off.

It may be well to emphasize at this point that, although certain general principles govern the treatment of diabetes as a disease, yet it is the duty of the practitioner to study each individual case separately, with special reference to his dietetic needs. It is only in this way that the disease can be intelligently treated. The patient should be weighed periodically, say every two weeks in private practice and twice weekly in hospital work, and a careful record kept. The patient's weight is the best single criterion we possess of the success of any line of treatment. This has especial reference to the dietetic treatment. No matter what the condition of the urine may be with reference to the presence or absence of sugar, the patient on any line of treatment must be regarded as doing badly if his weight is progressively diminishing. It is much better for the individual to excrete moderate amounts of sugar and hold or increase his weight, than to be aglycosuric and steadily lose weight. It is important to keep this axiom always in mind, particularly in regulating the diet. It is not infrequent to find that a diabetic will lose weight when on a non-carbohydrate diet and excreting no sugar or only small amounts, whereas he will begin to increase in weight if moderate amounts of carbohydrates be added, even though he excretes more sugar. This is probably explained by Leo's research, in which he showed that the administration of a certain amount of carbohydrates to a diabetic spared proteid metabolism.

The treatment of diabetes may be considered under four headings—hygienic, dietetic, medicinal, and treatment of the complications.

Hygienic.—It is very important to look after the personal hygiene of the patient. Daily baths assist materially in keeping the skin functions active, and diminish the liability to furunculosis. By personal cleanliness the distressing pruritus pudendi can be partially alleviated. To the thin diabetic, with a dry, harsh skin, the lukewarm bath is often soothing. The more robust patients can stand a cold bath. An occasional Turkish bath is useful in the obese cases, as it is a partial substitute for massage. Light woolen underwear should be worn. Moderate exercise should be taken, as a certain amount of muscular activity favors sugar combustion. Violent physical exertion should be avoided in the severe cases, as it tends to induce coma. Massage is useful, as it tones up the muscular system and thus probably aids carbohydrate metabolism. All sources of worry and anxiety should be eliminated as much as possible. More or less obstinate constipation is the rule in diabetes, and it is of the utmost importance that this should be corrected, as persistent constipation in severe cases is held by many to favor the development of coma.

Dietetic.—We have seen that the symptoms of diabetes are directly or indirectly dependent upon the hyperglycæmia, the grade of which is pretty accurately indicated by the amount of glucose excreted. Our object, therefore, should be to eliminate the hyperglycæmia if possible. This will be most quickly effected by cutting out of the dietary those constituents that are most readily converted by the digestive processes into grape-sugar—namely, the carbohydrates.

When a diabetic patient comes under observation, it should be the physician's first duty to ascertain the patient's capacity to warehouse carbohydrates, or, in other words, to determine his tolerance for carbohydrates. This is done by placing the individual for at least five days on a diet absolutely free from starches and sugar; that is, on a proteid-fat diet. In so doing his weight must be taken into consideration and the diet so arranged that it will provide approximately forty calories for each kilo body-weight. This can, as a rule, be fairly readily done—and in hospital work should always be done—as the proteid and fat percentage of the various foods is given in some of the standard works on dietetics. Knowing that 1 gram each of proteid and carbohydrates yields 4.1, and 1 gram of fat, 9.3 heat units, the caloric equivalent of the diet can be readily calculated. As the carbohydrates, which ordinarily provide the largest number of calories in our diet, are cut off, it will be seen that the proteids and fats must be largely increased to make up for this deficit. Before arranging the non-carbohydrate diet, the individual likes and dislikes of the patient should be ascertained, so as to secure one that will be most palatable and one that will likely be entirely eaten each day during the test. The following may be used as a "standard" diet for the tolerance test, subject, to be sure, to variations according to the patient's age, weight, and likes or dislikes for certain forms of meats:

Breakfast.—7.30 A. M. 120 grams (3iv) of beefsteak or mutton-chops without bone; two boiled or poached eggs; 200 cc. (3vj) of tea or coffee.

Lunch.—12.30 P. M. 200 grams (3vj) cold roast-beef, mutton, or chicken; 60 grams (3ij) celery, fresh cucumbers, or tomatoes, with 5 cc. (3j) vinegar, 10 cc. (3ij) oil, pepper and salt to taste; 20 cc. (3v) whisky (if desired); 400 cc. (3xii) of water or Apollinaris water; 60. cc. (3ij) coffee.

Dinner.—6 P. M. 200 cc. (3vj) clear bouillon; 200 grams (3vj) roast beef; 60 grams (3ij) lettuce with 10 cc. (3ij) vinegar; 20 cc. (3iv) olive oil, or three tablespoonsful of some well-cooked green vegetable, as spinach; three sardines a l'huile; 20 cc. (3iv) cognac or whisky (if desired), with 400 cc. Apollinaris water.

Supper.—9 P. M. 2 eggs, raw or cooked; 400 cc. Apollinaris or Seltzer water.

With the four meals at least fifteen grams (about 3iv) of butter should be used in making the gravies and with the eggs. No milk or sugar is permitted with the tea or coffee. Saccharin may be used to sweeten them. The time of taking lunch and dinner, of course, may be reversed. This daily diet should provide a person of 60 kilos (132 pounds) with a little over the requisite 2,400 calories for an individual of that weight. One precaution must be emphasized here. If the patient has been eating freely of starches these must be cut down slowly for two or three days before he is placed on the standard diet. Any sudden and radical change from one diet to another is liable to induce coma. As it has been found that a dog must fast five days before the glycogen of his liver has been all used up, it is well to keep the diabetic on the above diet for at least five days; by so doing it practically eliminates the possibility that any sugar excretion at the end of that time is derived from the stored-up glycogen of the liver.

While on this diet, the total amount of urine should be collected for each twenty-four hours, mixed, measured, and the sugar determinations made from a specimen of the twenty-four hour amount. The reduction in the sugar excretion is often very striking in the first twenty-four hours. If the patient becomes aglycosuric within the first five days the case may then be considered a mild form of the disease, and it is then desirable to ascertain how much starch can be added to his diet without sugar appearing in the urine; in other words, to determine his tolerance for carbohydrates. This is probably best done by allowing the patient a weighed quantity of plain white bread, which contains approximately about 55 per cent. of starch. For the first day 25 grams of bread may be allowed. If sugar fails to appear in the urine another 25 grams (a little less than 3j) may be added the next day and so on until glycosuria does develop. The formula for the tolerance is as follows: Tolerance = Standard diet + x grams starch, x representing the number of grams of starch the patient can take without sugar appearing in the urine.

If the patient continues to excrete sugar after being on the standard diet for five days, it indicates that he is suffering from a severe form of the disease. It further means that the tolerance for carbohydrates is entirely destroyed, and that the sugar eliminated in the urine is manufactured from his tissue-albumins. In the cases in which glycosuria persists after the patient has been on the non-carbohydrate diet for five days, Naunyn recommends that a "Hunger Tag," or hunger-day be instituted, during which time no food whatever is taken for twenty-four hours. In a certain percentage of these cases the patients will become aglycosuric as a result of the starvation-day. Naunyn's reason for establishing a hunger-day is to remove the hyperglycæmia even though it be for only twenty-four hours. By so doing he claims that the tolerance for starches is increased, and that it is then possible to give small quantities of starch without glycosuria

occurring, and, which, without the hunger-day, would not be warehoused. This increased tolerance is believed to be due to the tissues securing a temporary rest from sugar formation. The writer's experience with the hunger-day is that it is useless to advise it if the percentage of sugar is 0.5 or over as when it is that high the sugar rarely entirely disappears. In the treatment of diabetes it is most advisable to put them on such a standard diet at least every three months in order that their tolerance for carbohydrates may be increased.

The foods the diabetic should be warned against taking, excepting with the permission of the physician, are as follows: Bread of all sorts, wheaten, rye, and brown; all farinaceous preparations such as rice, sago, tapioca, hominy, semolina, arrow-root, and vermicelli.

Thick soups are to be avoided. Among meats, liver is about the only form to be prohibited, owing to the glycogen it contains. For the same reason, oysters are sometimes prohibited.

All starchy vegetables: Potatoes, turnips, parsnips, squashes, vegetable marrow, beets, corn, peas, and artichokes.

Beverages: Beer; the sweet wines and sweet aerated drinks. These are excluded owing to the sugar, and not to the alcohol, they contain.

Fruits: Grapes, dates, figs, currants, raisins, dried prunes and plums, and other dried fruits rich in sugar, should be forbidden. Certain fruits such as peaches, apricots, stewed green gooseberries, may be permitted in mild cases. Some authorities on this disease are inclined to be rather more lenient in regard to fruits. It is well to remember that *lævulose* (fruit-sugar) has been shown to be tolerated better by the diabetic patient than any other form of sugar.

Sugar for sweetening purposes must be omitted. Without the physician's permission, milk must not be taken.

The following foods the diabetic may take unconditionally: Soups: Bouillon, ox-tail, and turtle; broths; soups with marrow and eggs permitted. Fresh meats: All the muscular parts of the ox, calf, sheep, pig, deer, wild and domestic birds—roast or boiled—warm or cold, in their own gravy or in a mayonnaise sauce.

Internal parts of animals: Tongue, heart, brain, sweetbreads, kidneys, marrow-bones, served with non-farinaceous sauces.

Preserved meats: Dried or smoked meat, smoked or salt tongue, corned beef, American canned meats.

Fresh fish: All kinds of fresh fish, boiled or broiled, prepared without breadcrusts or cracker-meal and served with any kind of non-farinaceous sauce, preferably melted butter.

Preserved fish: Dried fish, salt or smoked fish such as codfish, haddock, herring, mackerel, flounders, salmon, sprats, eels, etc.; tinned fish, such as sardines in oil, anchovies, etc.; caviar.

Eggs: Raw or cooked in any way, but without any admixture of flour.

Fresh vegetables: Green lettuce, cress, spinach, cucumbers, onions, asparagus, cauliflower, red and white cabbage, French beans. The vegetables, as far as they are suited to this method of preparation, are best cooked with meat or a solution of Liebig's Extract and salt, and cooked plentifully with butter. The addition of flour is not permissible.

Preserved vegetables: Tinned asparagus, French beans, pickled cucumbers, mixed pickles, sauerkraut, and olives.

Spices: Salt, white and black pepper, Cayenne pepper, curry, cinnamon, cloves, nutmeg, English mustard, and capers.

Cheese: Neufchâtel, Edam, Stracchino, old Camembert, Gorgonzola, and other fat and so-called cream cheeses.

Beverages: All kinds of natural and carbonated waters, either clear or with lemon juice, or with rum, whisky, cognac, and cherry brandy. Light Moselle or Rhine wines, claret, dry sherry, or Burgundy, in amounts prescribed by the physician. Coffee, black or with cream, without sugar but sweetened with saccharin if desired. Tea, clear or with cream or rum.

From this list it will be seen that the number of articles not containing starch the diabetic may choose from, is quite extensive, and permits him to vary his dietary from time to time. In making up the "standard diet" certain of the articles in the above list may be substituted for some of those in the diet outlined.

Bread is the article of diet the cutting off of which the diabetic tolerates least well. Sooner or later a craving for it is inevitable. Various substitutes have from time to time been put on the market. The oldest of these and the one in most extensive use is *gluten bread* or biscuits made from gluten flour, first introduced by Bouchardat, in 1841. It is prepared by washing away the starch from wheat flour. The text-books on cooking give recipes for making bread and biscuits from this flour. Many firms claim to make pure gluten flour. Others are more conscientious, and state the percentage of starch their various preparations contain. It is easy to demonstrate that these gluten flours almost without exception contain starch, by adding a few drops of Lugol's solution. A blue, or even black, reaction is obtained, according to the amount of starch present.

Another substitute is bread or biscuits made from aleuronat flour, advocated by Ebstein and prepared by Dr. Hundhausen of Hamm, Westphalia, Germany. It is a vegetable albumin prepared by a special process from wheat. It contains from 80 to 90 per cent. of albumin in the dry substance and only 7 per cent. of carbohydrates. In making bread from it, a considerable percentage of starch has to be added.

Flours prepared from the soya bean, almonds, cocoanuts, and Iceland moss, have had their advocates as substitutes for wheat flour. The writer's experience has been limited to the use of gluten and aleuronat bread, and it has taught him that patients eventually tire of them and they still crave white wheat bread. Owing to the expense and the unreliability of most gluten flours, the writer has given up their use. It is much better to allow a diabetic to have daily a definite weighed quantity of white bread, the starch percentage of which we know to be about 55 per cent. It is well to have the bread thoroughly toasted. Well toasted graham bread may be used as a substitute with advantage.

Starch, in the form of potato, is thought to be more easily assimilated than wheat starch, and the comparatively recent work of Mossé seems to bear this out. The observations at the Johns Hopkins Hospital tend to confirm this view. Mossé allowed his cases 1 to 1.5 kilos (2 to 3 pounds) of potatoes daily. He says that there is a marked amelioration of all the distressing symptoms under the potato treatment. It is best to bake the potatoes. Naunyn does not speak very enthusiastically of this special cure in his last edition. He thinks that when benefits result, it is

due mainly to the fact that the diet in the case heretofore has not been properly arranged so far as the allowance of carbohydrates is concerned. Von Noorden recently has advocated very strongly a specially prepared oatmeal, and has claimed remarkable results in eliminating the glycosuria.

In the mild cases of diabetes (those that have become aglycosuric on the standard diet), the best course to pursue is to add to this standard diet weighed quantities of well-toasted white bread, the amount to vary with the tolerance of the individual. Occasionally, a roast potato may be substituted for the bread. In these cases milk is especially useful as it contains only between 4 and 5 per cent. of lactose which is very well assimilated by diabetics. A pint or a pint and a half, accordingly, may be permitted daily. The monotony of the standard diet may be from time to time relieved by making substitutes from the list of unconditionally allowable foods given above.

In the severe cases (those who fail to become aglycosuric on the standard diet) it, at first thought, would appear that the addition of carbohydrates would be contra-indicated as they would tend to increase the glycosuria, considering that the tolerance is *nil*. Experience, however, shows that these do better, and are more likely to hold their weight if given very moderate quantities of starchy food. The danger of coma is increased by any long continuation of an exclusive proteid-fat diet.

In both forms, a return to the strict diet, in order to increase the tolerance, should be made at least every three months for a period of ten days. It is desirable at shorter intervals in the severe forms.

No attempt should be made to restrict the water taken by the diabetic. No good will follow by doing so, as the thirst and polyuria are dependent on the hyperglycæmia. Harm, on the other hand, is likely to ensue, as the increased thirst causes increased mental and physical distress. Apollinaris and Seltzer water may be allowed, and the thirst may be quenched by drinking lemonade sweetened with saccharin instead of sugar. A drink made by dissolving a dram of cream of tartar in a pint of boiling water and flavoring with lemon peel and saccharin and then cooling, may be given freely for the same purpose.

Alcohol, in the form of whisky, cognac, or rum, is to be recommended as it aids fat digestion, and tends to make up for the loss in heat-units resulting from the cutting off of carbohydrates. One gram of alcohol by its combustion yields 7.0 calories.

Sawyer, of Cleveland, claims to have obtained marked benefit in diabetes by systematic gastric lavage.

Medicinal.—Few diseases have had a greater number of drugs advocated for their treatment; all of which goes to show that most of them are useless. In connection with no disease is quackery in and out of the profession more rampant. It is the duty of the practitioner, as much as possible, to discourage the patient from using the proprietary remedies so blatantly advertised in the daily press. These are all expensive and for the most part absolutely useless.

Only a few drugs have proven of any service whatever. The most useful is opium and some of its alkaloids. Its use in diabetes dates from the latter part of the eighteenth and beginning of the nineteenth century and particularly since its strong recommendation by Pelham Warren, in 1812. It is claimed that it diminishes the thirst, appetite, amount of

urine, excretion of sugar, and nervous irritability. As a consequence the weight increases and the general condition of the patient improves. Diabetic patients are unusually tolerant to opium and its alkaloids, and can take large doses without narcotism. By some, the crude opium, or the dried extract, are thought to give the best results. The patient may be started on half a grain of either, three times a day, and this may be increased until a total of from 4 to 6 grains daily are taken. Morphia, in increasing doses, has its advocates but the alkaloid now most extensively used in codeia. Half-grain doses of codeia sulphate after each meal may be administered at first, and increased until a total of 6 to 8 grains daily is reached. It is less constipating than the crude drug or morphia. There should be a gradual withdrawal of the opiates when the sugar is reduced to a minimum.

Arsenic stands next to opium in its apparent efficacy. It may be given as Fowler's Solution, commencing with 3 minims and gradually increasing up to 10, three times daily. Leube gives one-third of a grain of arsenious acid three times daily. In diabetes with marked functional nervous manifestations, bromide of potassium or soda is often useful. It tends to allay the nervous irritability and to diminish the glycosuria. The coal-tar products have been strongly advocated, and in neurotic cases antipyrine in 5 or 10 grain doses three times a day may prove useful. Potassium iodide should be given a thorough trial where strong suspicions of a luetic basis for the disease exist. Salicylates may be given where there are evidences of rheumatic arthritis. Uranium nitrate in recent years has been strongly advocated in certain quarters, but is uncertain in its effects. No attempt will be made to enumerate the multitude of other medicinal remedies that from time to time have been recommended. Drugs play a very minor part in the treatment of diabetes. The writer rarely resorts to them, excepting for the relief of special symptoms or complications.

Throughout the treatment, the urine should be regularly tested for the iron-chloride reaction for diacetic acid. If this be present, sodium bicarbonate in 2 to 3 gram (30 to 40 grain) doses, three times daily, should be administered. In this way the danger of coma may be averted.

Here also, brief reference to treatment at *mineral spas*, and by alkaline mineral waters, may be made. Of the spas abroad, those of Carlsbad, Neuenahr, Vichy, Marienbad, and Contréxeville, are probably the best for mild diabetics, and, particularly, for those in whom there are gouty manifestations. No severe case should be recommended to run the risks of a long, fatiguing journey to reach these places. Only too often a fatal termination is hastened. Undoubtedly, many mild cases are benefited. How much benefit is actually attributable to the waters themselves is difficult to determine. Undoubtedly, those that are mildly laxative, and those containing considerable quantities of carbonates and bicarbonates, thus tending to neutralize the abnormal acids of the blood, are helpful. There is no question, however, that the chief benefit is derived from the greater willingness of the patient to submit to a dietetic regimen, from the diversion and the freedom from business cares and worries. A bottle of Vichy or a couple of glasses of Carlsbad water daily may be taken with benefit in any part of the world. In the United States, mild cases may be benefited by a course at Saratoga Springs where the

Hathorn water is probably the best, at Bedford Springs, Pennsylvania, and, possibly, at Poland Springs.

Pancreatic preparations have been given a fair trial, but the results have been disappointing. This must necessarily be the case until we possess some clinical test by which we can recognize the cases due to pancreatic disease. Cammidge thinks this may be possible by his recently devised test. Pancreatic juice and extract have failed to produce any material benefit. Williams, of Bristol, transplanted the pancreatic gland of a sheep under the skin of the breast and abdomen of a diabetic. The patient died in three days of coma. Lépine advocated the use of pilocarpine, hypodermically, to stimulate the secretion of the pancreas, but without any satisfactory results. The same investigator, believing that diabetes is due to the failure of the pancreas to produce a necessary glycolytic ferment, produced such a ferment from malt diastase and administered it to several diabetic patients with apparent satisfactory results. Pancreatic therapy, up to the present, may be said to have yielded no beneficial effects. The recent investigations of Otto Cohnheim suggest that a combination of pancreas and muscle-juice may offer better prospects of success in the future.

Treatment of Complications.—(1) *Diabetic Coma*.—Certain factors predisposing to coma must be carefully guarded against. Obstinate constipation must be counteracted; prolonged restriction of a severe case to a diet entirely free from carbohydrates may tend to induce the complication. Sudden and radical changes from a mixed diet containing considerable starch, to a rigid diet, or vice versa, may precipitate it. We have seen that the coma is due to an acid-intoxication, the toxic agent being β -oxybutyric acid, derivative products of which are acetone and diacetic acid. Stadelmann, who first advanced the acid-intoxication theory, was also the first to recommend and use the alkaline treatment—the only one that has proved of any benefit. The existence of an “acidosis,” indicated by the elimination of either β -oxybutyric acid in the urine, or its product (diacetic acid), or an excess of ammonia, should at once be followed by the administration of sodium carbonate or sodium bicarbonate by mouth. The most serviceable clinical test for the “acidosis” is the ferric-chloride reaction for diacetic acid. If this be present, sodium bicarbonate, in 2 to 3 gram (30 to 45 grain) doses, three times a day, should be at once started. By so doing the acid-intoxication can be stopped, and the ferric-chloride reaction ceases to be obtained. The alkali neutralizes the acid in the circulating blood, and the tissue-bases (sodium, potassium, etc.), and the ammonia which is derived from the breaking down of the body-proteids are spared. In mild cases of acidosis, it is important to remember that the latter may be relieved by making moderate additions of carbohydrates to the diet if the latter has previously been very restricted. Although the presence of β -oxybutyric acid, or diacetic acid, in the urine must always be considered a danger signal of possible impending coma, occasional cases are met with in which they are present for months without apparent harm. Naunyn states that when the ammonia excretion reaches 4 grams daily, he has never seen a case in which it was possible to ward off an eventful attack of fatal coma.

When actual symptoms of coma have set in, treatment is almost hopeless, and the rule that prevention is better than cure is nowhere better

illustrated than in this dreaded complication. When coma symptoms do intervene, the most active treatment should be instituted, however. Carbohydrates should be added to the food if the patient is still able to swallow. We have already seen that acetone, diacetic acid, and β -oxybutyric acid are largely, if not entirely, derived from fat owing to the diminished power the tissues of the diabetic possess of properly oxidizing the fats of the food and tissues. The mildest grade of this defective power of oxidation manifests itself in the appearance alone of acetone in the urine; the medium grade with the appearance of acetone and diacetic acid; and the severest grade with the occurrence of both these, and an addition of β -oxybutyric acid. As coma supervenes the amount of acetone diminishes and the quantity of β -oxybutyric acid increases. The knowledge that the administration of carbohydrates will diminish or clear up the acidosis when it has not reached too severe a grade is one of the important recent advances in the therapy of diabetes. The administered carbohydrate in some peculiar manner favors the more complete oxidation of the fats. In the severest cases of diabetes, even those with coma manifestations, the organism never entirely loses its capacity to burn up carbohydrates. Milk is most valuable in these cases. From 500 to 1,000 cc. may be given in the twenty-four hours. Of all carbohydrates *lævulose* is most easily burnt up by the diabetic. Recently von Noorden has advocated the subcutaneous injections of 5 to 10 per cent. solutions of *lævulose* in cases with threatened coma. Naunyn prefers its administration either by mouth or by enema. Realizing the origin of the acetone bodies, the importance of cutting down the fats in threatened coma becomes at once apparent. Those containing the lower fatty acids are most injurious. The fats permitted should be chiefly those of vegetables and meats, as these contain comparatively little of the lower fatty acids. Butter, if used, must be given in limited quantities and only after having been thoroughly washed with water to remove the above acids. It is probably better to entirely exclude butter in the threatened coma cases, as it has been shown to very materially increase the output of the β -oxybutyric acid. Sodium carbonate, or bicarbonate, should be given by mouth, rectum, and intravenously, in enormous quantities. As much as 4 to 8 grams (1 to 2 drams) of sodium bicarbonate, every hour, by mouth, if deglutition is still possible, and double this quantity per rectum every two hours, should be administered. More effectual results will follow an intravenous alkaline injection. Enormous quantities of sodium carbonate have been introduced at one injection. Thus Minkowski gave 84, Lépine 44, Wolfe 30, and Rosenstein 20 grams at one operation. The temporary results are often striking. The respirations becomes quieter, and when the coma is not deep there may be temporary return to consciousness. As strong a solution of sodium carbonate as 3 to 5 per cent. has been used. In practically all these cases there is a recurrence of the coma in a few hours and death within twenty-four or forty-six. The custom at the Johns Hopkins Hospital has been to introduce a liter of a 2 per cent. solution of sodium bicarbonate in normal salt solution slowly into one of the median basilic veins, and to repeat the procedure on the opposite side in four or six hours. From 200 to 400 cc. of blood should be first removed. In a young girl of twelve, definite symptoms of commencing coma were, in this way, temporarily warded off, death resulting

a week later from typical coma. Intravenous injections of Ringer's solution have been recommended. Naunyn states that, once coma is well established, he does not think it possible permanently to relieve it. The grade of the acid-intoxication in these severe cases is indicated by the fact that, no matter how vigorously the alkalis are pushed, it is not possible to render the urine alkaline. Grünberger, in 1905, performed lumbar puncture in a coma case and found acetone and diacetic acid in the cerebrospinal fluid, although the urine was free from diacetic acid. Naunyn suggests that in these cases there may be a direct toxic action on the central nervous system and that the matter needs further investigation.

2. *Pruritus*.—Frequent bathing of the genitalia, to prevent them from becoming saturated with the saccharine urine, is the best preventive. Bathing with soda solution, or 100 to 200 solution of carbolic acid, may give some relief. The best remedy is a solution of boric acid or of hyposulphite of soda (30 grams or 1 ounce to the liter or quart of water), applied as a lotion. Ichthyol and lanolin ointment may give relief in some cases. Menthol ointment (grs. x to vaseline 3j) sometimes gives relief. These are purely local measures and the symptom will yield when the glycosuria is relieved by the usual measures.

3. *Gangrene and Carbuncle*.—As temporary measures, the affected parts should be dressed with bichloride compresses. Early amputation and excision, respectively, are indicated. There is a certain risk of either the anæsthetic or the operation itself precipitating coma, but this is much less than the danger from the complications, as both are liable in themselves to cause death by inducing coma.

CHAPTER XXX.

DIABETES INSIPIDUS.

By THOMAS B. FUTCHER, M. B.

Definition.—A chronic affection, characterized by the passage of large quantities of pale urine of low specific gravity, free from sugar, albumin, and casts, and usually accompanied by an insatiable thirst.

Although Thomas Willis, in 1674, first recognized a difference between a saccharine and a non-saccharine polyuria, it was Johann Peter Frank who, in 1794, first gave us a definition for diabetes insipidus when he described it as a long-continued, abnormally increased secretion of non-saccharine urine which is not caused by a diseased condition of the kidneys. He distinguished two forms of diabetes, a *diabetes insipidus*, or *spurious*, and a *diabetes mellitus*, or *verus*. In 1838, Robert Willis proposed the following classification of the diabetes insipidus cases according to the urea secretion: *Hydruria* included those cases where there was polyuria and a normal urea output; *azoturia*, those with polyuria and increased urea excretion; *anazoturia*, those with polyuria and diminished urea elimination. It is now well recognized that these do not represent distinct types of the affection.

Incidence.—Diabetes insipidus is a rare disease. In the seventeen years ending May 15, 1906, since the opening of the Johns Hopkins Hospital, there were 8 cases out of 106,000 ward and dispensary medical patients, or 0.007 per cent. Six of these were in-patients among 19,685 medical admissions, or 0.03 per cent. Among 113,600 patients treated at the Charité, Berlin, from 1877 to 1896, there were 55 cases, or 0.048 per cent. Eichorst observed 7 cases, or 0.02 per cent., among a total of 35,942 patients at the Zürich Hospital.

Etiology.—The majority of cases occur in comparatively *young persons*. Of 85 cases collected by Strauss, 9 were under five years; 12, between five and ten years; 36, between ten and twenty-five years. In van der Heijden's series of 87 collected cases, there were 7 in the first, 19 in the second, 23 in the third, and 19 in the fourth, decade. A *hereditary tendency* has been noted in certain cases. The most remarkable instance of the influence of heredity is in the family reported by A. Weil. Of 91 members of four generations, 23 had persistent polyuria without any deterioration of health, namely, the great grandfather, his three children, seven grandchildren, and twelve great grandchildren. Of the 22 affected descendants of the original case, there were 11 males and 11 females. The cases were congenital and persisted throughout life. Lacombe, Pain, and Gee, have reported similar instances of heredity in this disease. Males are more liable to the affection than females. Cases have been reported to be due to the effects of exposure, drinking copiously of cold

fluids, and a drinking-bout. Trousseau noted that it was not unusual to find that the parents of patients suffering from diabetes insipidus were either albuminuric or glycosuric. Ralfe emphasized the frequency with which a history of tuberculosis, syphilis, and gout, were obtained in one or both parents.

Before proceeding with an account of the organic lesions that have been found in many of the cases of diabetes insipidus, it may be of some assistance, in showing their bearing on this affection, briefly to outline the results of the work done on *experimental polyuria*. In 1849, Claude Bernard demonstrated that there was a point in the floor of the fourth ventricle of animals, just in front of the "glycosuric" centre, injury of which frequently produced a simple polyuria, but occasionally also an accompanying albuminuria. Eckhard, from 1869 to 1872, published the results of his experiments, which were more elaborate than those of Bernard. He found that the vagus had no influence on the secretion of urine in dogs or rabbits. Cutting of the greater splanchnic nerve in dogs produces an immediate increase in the urinary secretion, the amount being about four times that normally eliminated. Stimulation of the peripheral end of the cut splanchnic stopped the increased elimination. He concluded that the greater splanchnic is the vasomotor and special secretory nerve of the kidney in dogs. Section of the spinal cord at the level of the sixth or seventh vertebra, as well as at higher levels, produced, without exception, an immediate and persistent suppression of the urine. He therefore inferred that the centre regulating the urinary secretion is above this level. The nerve fibers supplying the kidneys were found to pass from the medulla in the cord to the level of the sixth or seventh cervical vertebra, where they leave by the upper thoracic nerves, whence they pass along the walls of the aorta and renal arteries to the kidneys. In rabbits, Eckhard found that stimulation of points in the floor of the fourth ventricle—other than Bernard's "polyuric" centre—occasionally produced an excessive flow of urine. In these animals, also, he found that injury of the vermiform process of the middle lobe of the cerebellum occasioned polyuria. This was most readily produced by injury of the most posterior of the convolutions of the middle lobe of the cerebellum seen from above. To this convolution Eckhard gave the name "*lobus hydruricus et diabeticus*"—"diabeticus" because the polyuria was frequently accompanied by glycosuria. Deep injuries of the posterior lobe of the rabbit's brain (that occupying the concavity of the temporal bone) were occasionally followed by polyuria. Kahler made further valuable contributions to the subject in 1886. By injecting minute quantities of a concentrated silver-nitrate solution into various regions of the brain, he was able to cause lesions which produced either a temporary or permanent polyuria. He found that, whereas lesions of the middle lobe of the cerebellum produce a more or less temporary polyuria, wounds of the medulla oblongata, on the other hand, are followed by a permanent polyuria. The corpus trapezoides of the pons, and the lateral part of the exposed portion of the medulla oblongata, were the areas, injury of which was most likely to produce a permanent polyuria. The portion of the rabbit's brain just designated corresponds in the human brain with the area of the pons where the sixth and seventh cranial nerves make their exit from the brain. This throws some light on the cause for the existence of paralysis of the sixth nerve,

occasionally seen in diabetes insipidus. Kahler also found that destruction of the inner part of the cerebellum with Dieter's nucleus and its caudal processes, causes, practically always, a permanent polyuria.

From this experimental work it would appear that in dogs or rabbits a simple polyuria is most likely to result from the following lesions: (a) By injury of a point in the floor of the fourth ventricle a little anterior to Claude Bernard's "glycosuric" centre; (b) injuries to various portions of the middle lobe of the cerebellum, particularly the "*lobus hydruricus et diabeticus*" of Eckhard; (c) by lesions of the corpus trapezoides of the pons and the lateral part of the exposed portions of the medulla oblongata; (d) by cutting the greater splanchnic nerve in dogs.

By analogy, we would expect that lesions in these situations in man would produce a simple polyuria, although positive conclusions must not be drawn. We can see how tumors occupying the medulla or the base of the brain, or a basilar meningitis of syphilitic or other origin, could be capable of producing symptoms of diabetes insipidus in the human subject.

The immediate cause for the polyuria in the above experiments is not definitely settled. Although Eckhard claimed he had demonstrated special secretory nerves for the kidney, all the leading modern physiologists deny the existence of such nerves, as they have never been demonstrated to enter the renal cells, and they believe the polyuria results from increased blood pressure. The possible effect on the urinary secretion of remote lesions of the nervous system was clearly stated by Ralfe in the following terms "It is interesting to trace the course of the nerves forming the renal plexus, as irritation from eccentric or distant sources may play a part in inhibiting the renal nerves. Thus the nerves forming the renal plexus are derived chiefly from the solar plexus; as the right vagus and greater and lesser splanchnics join the solar plexus, it is probable that branches of these nerves enter the kidney by way of the renal plexus. The splanchnics, also, send branches direct to the renal plexus, and the left vagus sends some fibers to the left kidney. They contain medullated and non-medullated fibers; and Krause has traced the latter as far as the apices of the papillæ. Their mode of termination is unknown. Physiologically, vasoconstrictor, vasodilator, and sensory nerves, have been ascertained. The connection through the vagus brings us into range with the medulla oblongata, and with many organs susceptible of tubercular or syphilitic growths, or of sudden shock, such as a chill. The solar plexus may propagate the effect of abdominal new-growths or aneurisms."

We are now in a better position to understand the effect of the various lesions found in diabetes insipidus. According to Stoermer, traumatism to the brain is the cause in 30 per cent of the cases. Trauma of the soft parts has not the same effect. The only authentic exception is a case reported by Nothnagel in which the affection followed a kick on the abdomen. In traumatic injuries of the brain it does not seem essential that any special part of the brain be involved. The polyuria seems to result from the effects of the concussion the brain sustains. In 1865, Leyden reported a case following cerebral hemorrhage, and Ollivier subsequently drew attention to the comparative frequency of hemorrhage as a cause. Van der Heijden saw a case in chronic hydrocephalus. It has been observed in general paresis, and has followed the effects of otitis media. Cerebral tumors rank at the head of the list of gross brain lesions in the frequency

with which they are followed by diabetes insipidus. The nature of the tumor is a minor factor. It may be a gumma, a malignant growth, or a tuberculous focus. Diabetes insipidus is more likely to follow where the tumor involves the floor of the fourth ventricle, or the immediate vicinity.

The writer has been impressed recently with the importance of cerebral syphilis as a cause of the affection, having recently reported 9 cases of diabetes insipidus, in 4 of which, from the history, symptoms, and the improvement under potassium iodide, it seemed without doubt that cerebral syphilis was the cause. In 1 of these the lesion was a gumma, and in the other 3, the symptoms pointed toward there being a basilar syphilitic meningitis as a part of the syphilitic lesion. Polyuria and polydipsia have long been described as symptoms of cerebral syphilis. Fournier reported 6 cases in which these symptoms were present in association with various cerebral manifestations of the disease. Lancereaux, Oppenheim, and others, have noted the association. The lesion usually producing the polyuria is a basilar syphilitic meningitis. This was the form of lues in Buttersack's case, in which the disease was localized mainly in the interpeduncular space. Polyuria was the initial symptom in his patient. Nonne states that it is not necessary, as was formerly held, that the lesion should involve the medulla oblongata or its vicinity. He asserts that all we can say is that polyuria and polydipsia are most liable to occur in syphilitic brain lesions which manifest themselves in the form of a diffuse basilar meningitis. One can appreciate how a basilar meningitis might cause a polyuria, when one recalls that, in experimental polyuria, it was shown that injuries to the middle lobe of the cerebellum, and to the superficial areas of the pons and medulla, caused a profuse flow of urine.

Many of the cases of diabetes insipidus due to basilar syphilitic meningitis have been associated with a peculiar form of bilateral hemianopsia. Oppenheim considers an "oscillatory" form of hemianopsia or "hemianopsia bitemporalis fugax" as being practically pathognomonic of this particular lesion. He has reported 3 such cases, in 1 of which polyuria and polydipsia were associated. Spanbock and Steinhaus state that in 50 collected cases of temporal hemianopsia, there was polyuria in 11. The hemianopsia comes and goes several times in the twenty-four hours, and such a history was obtained in 2 of the 4 cases of diabetes insipidus with cerebral lues reported by the writer.

Hadra and Ralfe have reported cases accompanying aneurism of the carotid and of the abdominal aorta respectively. The affection has not infrequently been noted in affections of the abdominal viscera. In 1794, Frank observed a fatal case in a patient with chronic disease of the intestine. Schapiro reported 5 similar cases from Eichwald's clinic. Dickinson recorded an instance in a patient with carcinoma of the liver with secondary metastases in the retroperitoneal lymph glands, which had involved branches of the solar plexus.

Affections of the spinal cord have, in rare instances, been regarded as the cause of the disease. Schlesinger saw a case in a patient with tabes. In a case of Westphal's, it occurred in association with spastic spinal paralysis. F. Schultze saw a case in a patient with a diffuse tumor of the cord. Instances of persistent polyuria have been observed by Krauss in syringomyelia, and by Friedreich in hereditary ataxia.

Diabetes insipidus has been known to follow the infectious fevers. Thus, it has been observed after typhoid, typhus, diphtheria, measles, and scarlet fever.

In very rare instances, a diabetes mellitus may pass over into a diabetes insipidus. This is most likely to occur after traumatism to the brain, in which, at first, sugar accompanies the polyuria, but later disappears, leaving the characteristic urinary features of diabetes insipidus. Occasionally, however, diabetes insipidus may pass over into diabetes mellitus. In 1897, Senator reported such a case in a woman, aged forty-three years, who, since childhood, had voided daily from 12 to 15 liters of urine of a specific gravity of from 1,001 to 1,003, and who developed a mild glycosuria. Three years before her death 0.3 per cent. of sugar was found in her urine. No organic lesions were detected at autopsy.

Clinical Classification.—The disease may be divided clinically into two groups: (1) The primary or idiopathic cases. This group includes the cases in which there is no evident organic basis for the disease, and comprises a considerable percentage of the total. (2) The secondary or symptomatic cases. These include the cases in which there is evidence of organic disease of the nervous system or elsewhere, the lesion being considered the cause of the polyuria.

Symptoms.—The disease may begin abruptly, as after a severe fright. More commonly it develops slowly. Polyuria is the most constant and characteristic feature. The quantity of urine passed daily may be enormous. Troussseau had a patient, aged twenty-four years, who passed 43 liters in a day. The weight of the urine voided daily may almost equal that of the patient. Thus, Vierordt cites an instance of a child weighing 13.2 kilograms, voiding 12.3 kilograms of urine daily. The largest daily elimination in any of the writer's 9 cases was 16.5 liters. One passed 1,700 cc. at a single voiding. The urine is usually almost colorless. It may have a bluish tint. The specific gravity generally ranges between 1,001 and 1,005. It may be much higher, if there is a marked excretion of urea. Thus Laparguiois observed a case in which 6 liters of urine was passed daily with a specific gravity of 1,017. The urine is usually free from albumin, sugar, or casts. Occasionally, traces of albumin may appear in the late stages. In the early stages the output of urine may far exceed the intake of fluids. This is due to withdrawal of fluids from the tissues. The writer has noted this inequality in cases of long standing. Dickinson conducted experiments suggesting that this was in part due to absorption of the moisture of the air through the skin. The balance of opinion favors the view that a condition of "bradyuria" rather than "tachyuria" exists in this disease. In other words, when a copious draft of fluid is taken, an increase in the flow of urine is slower in making its appearance, and the total elimination is slower in a patient with diabetes insipidus than in a healthy individual. There is a slight increase in the urinary solids in the majority of cases. The urea may be markedly increased, but this is due to the food ingested, rather than to any increased tissue metabolism. The chlorides are sometimes increased. Muscle-sugar, or inosite, has been frequently demonstrated in the urine. This is believed to result from the flushing out of the muscles by the enormous quantity of fluids taken.

Thirst is practically a constant and often a distressing symptom. In many cases it is the first one complained of, as it first attracts the patient's attention. One patient of the writer said he "simply lived to drink," and described the infinite satisfaction it gave him to be able to take a whole pitcher of water at one draught. Trousseau's patient drank 50 liters in twenty-four hours. In experiments in which the fluids have been cut off, the patient, as in Strubell's case, has been known to drink his own urine. It is very difficult in many cases to determine, from the history or otherwise, whether one is dealing with a primary polyuria or a primary polydipsia. These can scarcely be considered independent diseases, however. Nothnagel's case is usually cited as a typical instance of a primary polydipsia. A man, aged thirty-five, was kicked in the abdomen and fell, striking his head in the region of the right ear, against a stick of wood, but was not rendered unconscious. Half an hour later he began to have intense thirst and drank three liters of water, but it was not until about three hours afterward that the first urine was voided. Buttersack gives the following conditions as indicating a primary polydipsia in any particular case: (1) There is normal sweat secretion. (2) The urine is less than the amount of fluids taken. (3) The polyuria ceases on cutting off the fluids. (4) The urine elimination and liquids taken run parallel. Stermer states that in primary polydipsia the blood is of normal concentration, while in primary polyuria it is increased.

The appetite varies considerably in different cases. Often it is not increased, and may be diminished. On the other hand, it may be ravenous, as in Trousseau's patient, who ate in the Paris restaurants, where the meals were a fixed price and the bread was not charged for. He devoured so much of the latter that it was more profitable for the restaurant keepers to pay him to remain away. These bulimia cases are the ones in which there is such a marked increase in the ura output. Absence of sweating is the rule. The insensible perspiration is also diminished. Constipation is common. Cataract has been described. One of the writer's patients had bilateral plaques of xanthoma palpebrarum. As already stated, there may be recurring attacks of transitory bitemporal hæmianopsia in cases due to basilar syphilitic meningitis. Choked disk may be present. Paralysis of the sixth nerve is sometimes seen. Many of the cases due to cerebral disease have intense headaches. Some suffer early and throughout the disease, with racking pains in the back and legs. In one of the writer's cases there were several attacks of transitory left-sided hemiplegia, followed by an attack of longer duration, from which it took weeks to recover. Impotence not infrequently occurs. Marked emaciation may develop in the secondary symptomatic cases. In the idiopathic cases, on the other hand, there may be no loss in weight. Œdema of the feet may occur in the last stages of the asthenic cases. In contrast to diabetes mellitus, the knee-jerks are likely to be exaggerated. Of 9 cases, they were exaggerated in 5, normal in 1, diminished in 2, and not noted in 1. The results of researches show that metabolism is but little disturbed, notwithstanding the abnormal fluid exchanges. In some of the cases the blood is concentrated and the red cells may be between six and seven millions per cmm. The temperature is always subnormal, unless some complication intervenes. During febrile attacks the amount of urine may diminish considerably. The pulse is usually of small volume,

and there is said to be no increase in the blood pressure. Toward the end the exhaustion may be extreme. Death is sometimes preceded by an uncontrollable diarrhoea. Drowsiness eventually ensues, and death occurs with the patient in coma. The immediate cause in many cases is a low form of congestive pneumonia.

Morbid Anatomy.—There are no lesions peculiar to the disease. The various morbid processes found at autopsy, and already given in the section on etiology, are primary rather than secondary. The kidneys are usually enlarged and hyperemic. The bladder is dilated, and its walls hypertrophied. Dilatation of the ureter and pelves of the kidneys is occasionally found.

Theories as to Cause.—The essential cause for the polyuria has been the subject of much research, and is still far from being satisfactorily explained. However it may be brought about, the determining factor seems to be a disturbance of the secretory function of the kidneys. Osler says that "it results from a vasomotor disturbance of the renal vessels, due either to local irritation, as in the case of an abdominal tumor, to cerebral disturbance in cases of brain lesion, or to functional irritation of the centre in the medulla, giving rise to continuous renal congestion." Dietrich Gerhardt states that in the idiopathic forms "the disease is due to a disturbance of the secretory function of the kidneys and not to an increase in the thirst or to blood changes." Meyer, in a research published from Müller's clinic in May, 1905, comes to the conclusion that in diabetes insipidus one has to do with a primary polyuria, which results from an incapacity of the kidneys to secrete a urine of normal concentration. In consequence of this functional incapacity of the kidneys, the diabetes insipidus patient, in order to eliminate the end-products of tissue metabolism circulating in the blood, has to imbibe larger quantities of water than does the normal individual. Thus, the administration of sodium chloride to a patient with primary polyuria is not followed by the elimination of a urine of increased specific gravity, the quantity of urine being actually increased. In primary polydipsia on the other hand, according to Meyer, the power of the kidneys to secrete a more concentrated urine is not destroyed. Thus, the administration of sodium chloride to such a patient is followed by an increase in the specific gravity, without any increase in the volume of the urine.

Diagnosis.—There is no arbitrary line separating the physiological from the pathological polyurias, so far as the amount of urine is concerned. The chief distinguishing features of the polyuria of diabetes insipidus is its permanence, a physiological polyuria usually being transitory. The greatest difficulty will arise in distinguishing the cases from those of chronic interstitial nephritis, where an abundant, pale urine is common. In the latter, the existence of albumin and a few casts, with certain cardiovascular features, should not cause much difficulty. The hysterical polyuria will usually be recognized by the existence of certain nervous and psychical symptoms. The polyuria, further, is likely to be intermittent in character. Some have included hysterical polyuria as a form of diabetes insipidus, but this hardly seems justifiable. The absence of sugar and the low specific gravity differentiate the affection from diabetes mellitus. Whether or not "primary polyuria" and "primary polydipsia" should be considered as two distinct affections is doubtful. The writer's feeling is

that they should not, as the clinical features in the two are practically identical. As stated, Meyer holds that, in the former, the kidneys are incapable of secreting a more concentrated urine on the addition of sodium chloride, etc., to the diet, whereas this capacity is not destroyed in the latter.

Prognosis.—Idiopathic diabetes insipidus is much the more benign of the two forms. There is usually no marked emaciation, and the cases have been known to last for fifty years. The prognosis is less favorable in the secondary or symptomatic cases. Emaciation is often rapid and an early fatal termination may ensue. The length of life depends largely on the seat and nature of the organic lesion causing the polyuria.

Treatment.—This is on the whole most unsatisfactory. Once the polyuria is established, it is practically impossible permanently to relieve it. The long list of drugs recommended is ample evidence of their general inefficiency. Preparations of opium have been used with some benefit. The crude opium or extract, in half-grain doses, three times daily, and gradually increasing until a total of 4 to 6 grains daily are taken, may be tried. Codeia may be administered in the same way. The relief, palliative rather than curative, is probably due to the lessening of the sense of thirst. The commonest drug administered is valerian. Either the powdered root, given at first in 5 grain doses, three times daily, and increased until the patient takes a total of 2 drams, or the valerianate of zinc in 15 grain doses, increased to 30 grains three times daily, may be tried. Preparations of ergot have a good reputation, and to a certain extent, justifiably so. Ten minims of the tincture or fluid extract, three times daily, may be tried, and it is not infrequently followed by an appreciable reduction in the amount of urine. The benefit is temporary and symptoms of ergotism must be guarded against. According to Erich Meyer, theocin seems to increase the functional activity of the kidneys. After its administration, the specific gravity is increased, and there is no increase in the amount of urine. It may be given in 0.3 gram (5 grain) doses, three times daily.

As it is probable that a larger percentage of cases are due to cerebral lues than is generally supposed by the profession, a luetic history should be carefully inquired for, and late syphilitic manifestations searched after. Where there are marked cerebral symptoms, potassium iodide and mercurial inunctions should be given a thorough trial. In the 4 of 9 cases in which syphilis was believed to be the cause of the disease, there was marked improvement in the cerebral manifestations, in the general health, and a striking increase in the weight, in all instances after a thorough course of luetic treatment. There was, however, no material diminution in the amount of the urine.

These are the drugs which experience has shown to give the best results. The long list of other remedies that have been tried will not be enumerated.

It is not advisable to greatly restrict the liquids. When a patient first comes under observation, it is well to reduce the fluids a pint a day, so long as there is a corresponding reduction in the amount of urine. When the reduction of urine ceases to follow the reduction in fluids, no further limitation of the latter should be made, as it means that the patient is abstracting fluids from his own tissues. For the thirst, the usual acidu-

lated drinks may be tried. If the digestive powers are good, there is no occasion for any special limitation of the food. Strongly salted meats should be avoided, as they will tend to increase the thirst and, consequently, the polyuria. Meyer holds that meats in general should be restricted. They yield more products which are ordinarily excreted by the kidneys than do the other foodstuffs, and a diet liberal in meats would tend to aggravate the symptoms, since the patient would have to drink more freely of water in order to produce a solution of these products sufficiently dilute for the kidneys to be able to excrete them.

The tendency to constipation should be counteracted, and it is advisable to place the patient on a good general tonic.

CHAPTER XXXI.

GOUT.

By THOMAS B. FUTCHER, M. B.

Definition.—A nutritional disorder, characterized by disturbances in nitrogen metabolism, with an excess of uric acid in the circulating blood, and, usually, by an arthritis, the distinguishing feature of which is the deposition of sodium biurate in the peri-articular cartilages and tissues.

Historical.—The writings of Hippocrates, who lived about 350 B.C., show that he was familiar with the symptoms of gout. Celsus and Galen also, had some knowledge of the affection. Aretæus, who wrote about the middle of the second century of the Christian era, classified the disease according to the part affected, and called it Podagra, Gonagra, and Chiragra, when the attack seized the foot, knee, and hand, respectively. He also mentions that a gouty patient has, during the interval between the acute attacks, even won in the Olympic games. These early writers were also familiar with the hereditary nature of the affection. The name gout (*gutta*, a drop) was introduced by Radulfe at the end of the thirteenth century. It owes its origin to the prevailing belief that the disease was due to the presence in the blood, of some peculiar humour which is thrown out, or, as it were, distilled into the joints, drop by drop. Thomas Sydenham (1624–1689), who was himself a martyr to the affection, gave us an account of its clinical symptoms that has never been surpassed. In 1776, Scheele and Bergmann first discovered uric acid in vesical calculi and in human urine. The association between uric acid and gout dates from 1797, the year in which Wollaston demonstrated that the gouty deposits about the joints contained uric acid. Garrod, in 1848, by his well-known thread-test, demonstrated uric acid in the circulating blood of gouty individuals.

Incidence.—Gout is not so rare a disease in this country as the text-books would lead us to suppose. If physicians will recognize the fact that there is, probably, no such affection as chronic rheumatism, and that the vast majority of cases of chronic arthritis are either gout or arthritis deformans, it will be found that, with due regard to the points in the differential diagnosis, a great many more cases will be justly attributed to gout than has been the case in the past. In the first seventeen years since the opening of the Johns Hopkins Hospital, ending May 15, 1906, there have been 63 cases of gout among a total of 19,685 medical admissions, or 0.32 per cent. A comparison between the number of gout admissions to the Johns Hopkins Hospital and those admitted to St. Bartholomew's Hospital, London, for fourteen years showed that the ratio was just 2 to 3. Considering that gout is more prevalent in Southern England than anywhere else in the world, it indicates that in the vicinity of Baltimore,

at least, the disease is only one-third less frequent among hospital patients than in London. It must be remembered that the better classes, in which it is more common, do not usually seek hospital treatment.

Etiology.—1. Predisposing Causes.—(a) Heredity.—Hereditary predisposition is, undoubtedly, one of the most important factors and plays a part in from 50 to 75 per cent. of the cases. This is particularly true with the well-to-do class. Scudamore states that out of 523 gouty patients, 309, or 59 per cent., gave a history of the disease in the parents or grandparents. Garrod found that the predisposition was inherited in 50 per cent. of his hospital patients. In his private cases, however, he believed that the tendency was inherited in 75 per cent. In the Johns Hopkins Hospital series of 63 cases, there was a history of gout or "rheumatism" in 20, or 31 per cent. It would appear, therefore, that gout in the United States is acquired or "free-hold," rather than inherited or "copy-hold," to use the classification of old Sir William Browne. It is an interesting feature that, although the women of gouty families may escape gouty manifestations, they are more likely to transmit the disease to their offspring than are the men. A grandson may inherit gout from a gouty grandfather through a mother who has never shown any manifest symptoms of the disease. Gout acquired from extrinsic causes may be transmitted to the offspring.

(b) Age, Sex, and Race.—Although, in inherited gout, infants at the breast have shown manifestations of the disease, it is a rare affection in infancy and childhood. This is illustrated by Scudamore's statistics of 515 cases, in which only 4 occurred before the age of seventeen, the youngest being eight years old. There were but 13 in the first two decades. When gout appears in a very young person it is nearly always inherited. In our series of 63 cases, the ages on admission to the hospital, according to decades were as follows: One to ten, none; eleven to twenty, 2; twenty-one to thirty, 4; thirty-one to forty, 13; forty-one to fifty, 17; fifty-one to sixty, 18; sixty-one to seventy, 7; seventy-one to eighty, 2. Although this analysis shows the largest number of cases in the sixth decade, that is, between fifty-one and sixty years inclusive, general statistics indicate that the initial attack makes its appearance most frequently in the fourth decade, namely, between the ages of thirty-one and forty.

Males are much more liable to the disease than females. In fact it is rare in women until after the child-bearing period is over. Since the time of Hippocrates, the relative immunity in women has been attributed to the influence of the catamenia. Of 80 cases collected by a special commission of the French Academy, only 2 were in females. Of 124 cases admitted to St. Bartholomew's Hospital, in fourteen years, 24 were in women. In our series of 63 cases, there were only 2 in females. Gout in women is usually inherited. Their relative immunity is undoubtedly due, in large part, to their not being exposed to the exciting factors to the same extent that men are.

The colored race does not escape. In the Johns Hopkins Hospital series there were 3 male negroes. Two came to autopsy and the biurate deposits were found in the joint cartilages, and in the third there were numerous tophi in the ears in which the sodium biurate crystals were demonstrated.

(c) *Alcohol*—It is probable that alcohol heads the list in importance among the predisposing causes. It is a curious fact that the fermented beverages, such as wines, particularly port and sherry, beer, ale, and porter, are much more injurious than the distilled liquors—whisky, brandy, rum, and gin. The quality of the alcohol seems to be, therefore, as important as the quantity. In Scotland, where whisky is the prevailing drink, gout is much less prevalent than in Southern England, where beer is the chief beverage. Investigation has failed to explain this difference in the action of the alcohol. It is apparently not due to the greater acidity of the fermented beverages, nor to the greater percentage of sugar or salines contained in them. Although the lighter beers of this country are considered less potent as an etiological factor than the heavier beers of England and Germany, the analysis of our series seems to show that beer is the chief etiological factor in the United States.

A very important contribution to our knowledge as to how alcohol acts injuriously in disturbing uric acid metabolism, has recently been made by Beebee, in Chittenden's laboratory. It was found that if a patient be put on a diet containing a definite quantity of purin or nuclein containing food and while on this diet he is given alcohol, there is an immediate increase in the output of uric acid in the urine. The alcohol, however, did not produce this result when taken with a light diet, or with one free from purin compounds. In other words, the alcohol only influences that portion of the uric acid which is derived from the ingested food, that is, the "exogenous" uric acid. Alcohol is well known to interfere with oxidative processes in the liver. Schittenhelm has shown that the liver and other organs contain an enzyme "*oxidase*," which has the power of oxidizing uric acid into urea and other products. It is quite probable that the increase of the uric acid in the blood and urine, after the ingestion of alcohol and purin-containing food, is due to the inhibitory action of the alcohol on this oxidase which normally oxidizes the uric acid into urea. The failure of the enzyme to effect this transformation, results in an excess of uric acid in the blood and consequently also in the urine. This important work explains how a rich proteid diet, together with the consumption of alcoholic fluids, predisposes to the development of gout.

(d) *Food and Exercise*.—Gout undoubtedly is a penalty of high living. Rich, nitrogenous foods, particularly the red meats and game, have always been held to be specially injurious. There is a growing tendency, however, to place less importance on the quality of the food and more on the quantity, and habits as regards to exercise. Overeating and the leading of a sedentary life are probably most important factors. Sydenham stated the case clearly when he wrote: "Great eaters are liable to gout, and of these the costive more especially. Eating as they used to eat, when in full exercise, their digestion is naturally impaired. Even in these cases, simple gluttony and free use of food, although common incentives, by no means so frequently pave the way for gout as reckless and inordinate drinking." Neither the quality of the food nor its quantity does so much harm as the fact that it is "unearned by muscular exertion," as Ewart puts it. We must remember that gout is not confined to the rich, however. Osler says: "In England the combination of poor food, defective hygiene, and the consumption of excessive malt liquors, makes 'the poor man's gout' a common affection." These were the conditions that

largely prevailed in our series, as 55 of the 60 patients were treated in the public wards, and belonged to the poorer classes.

(e) *Effect of Lead*.—Musgrave, Huxham, and Falconer (1772), had called attention to the association between lead poisoning and gout, but it remained for Garrod to show the importance of lead as an etiological factor. He found that 33 per cent. of the gout patients that came under his care in hospital practice, had at some period of their lives suffered from lead poisoning, and had for the most part been plumbers or painters. Only 3 in our series showed positive evidences of lead poisoning. One had lead colic, and 2 had a blue line on the gums. Seven others, however, had occupations exposing them to possible lead infection. Of the 9 patients, 6 were painters, and 3 were tinnerns. Thus in 9 of the 60 cases, or 15 per cent., lead was probably a contributory etiological factor.

We do not know in just what way lead infection predisposes to gout. Garrod found that the blood of patients suffering from lead poisoning contained an excess of uric acid. He pointed out also that these patients were liable to develop chronic nephritis, and drew the conclusion that the increased amount of uric acid in the circulating blood resulted from a renal insufficiency. The majority of subsequent investigators have supported this view. Sir Dyce Duckworth holds that the lead acts injuriously through its effects produced on the nervous centres. As will be seen later, Duckworth supports the nervous theory of the origin of gout.

(f) *Occupation and Physique*.—As stated, those whose occupations bring them into constant contact with lead, such as painters, plumbers, and enamelers, and to a less extent, tinnerns, are specially liable to be attacked. Bartenders and employees in breweries, owing to the opportunity for free indulgence in the use of malt liquors, are also very prone to the disease.

It is a conspicuous fact that one rarely sees gout in a weakly, undersized, and poorly nourished individual. Persons of large frame, good physique, and with a tendency to obesity, are the ones who usually manifest the disease, and seem particularly susceptible to the baneful influence of the predisposing factors already considered.

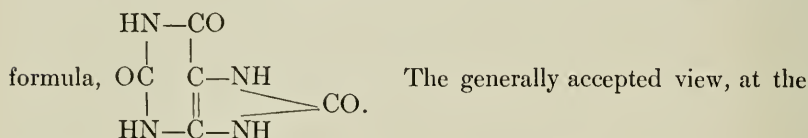
(g) *Traumatism* is thought by many to be a contributory factor. The prevalence of the attacks in the big toe joints has been in part explained by the liability of this articulation to injury while walking or from pressure by an ill-fitting shoe.

II. Metabolic Causes.—From the chemical standpoint, the etiology of gout is closely connected with nitrogen metabolism, and with the formation and excretion of certain compounds of which nitrogen is a component. Since 1797, the year in which Wollaston demonstrated that the gouty deposits about the joints contained uric acid, the vast majority of those who have studied the disease have concluded that it is connected in some way with the formation and elimination of uric acid. There is a steadily growing conviction among the best students of this disease at the present day that uric acid plays little or no part in the actual etiology of gout. Although an excess of uric acid in the blood and of its salts in the tissues dominates the picture in well-marked cases, this excess of uric acid is held to play a secondary part and to be a mere weapon of the disease. There is no experimental proof showing that an excess of uric acid causes any special toxic symptoms. The growing belief is that gout is

really a disease of intermediary purin metabolism. This view receives added support from the very important recent discovery that certain tissue ferments play a most important role in the metabolism of the purin bodies. While it will seem hard for us to divorce our minds from the long prevailing uric acid theory of gout, the following considerations of purin metabolism indicate strongly that we shall probably have to do so.

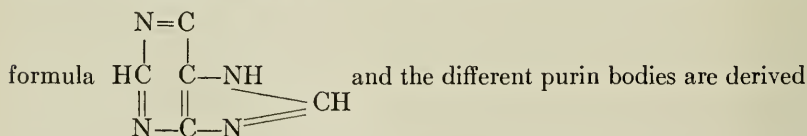
(a) *Uric-Acid Metabolism under Normal Conditions.*—To better appreciate the metabolic disturbances in gout, it is important to understand, as fully as our present knowledge permits, the chemistry of uric acid and its closely allied compounds under physiological conditions.

Uric acid has the empirical formula, $C_5H_4N_4O_3$ and the rational

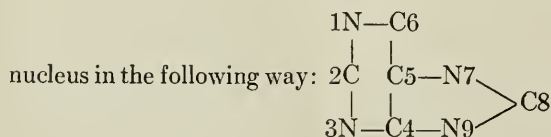


present time, is that it is derived partly from nuclein resulting from the disintegration of cell nuclei, and partly from the hypoxanthin, which is produced as a product of muscle metabolism. At least 4 other nitrogenous compounds are known to be derived from nuclein. These are xanthin ($C_5H_4N_4O_2$), hypoxanthin ($C_5H_4N_4O$), guanin ($C_5H_5N_5O$) and adenin ($C_5H_5N_5$). In addition to these, there are 5 other compounds closely allied to them in general structure. They are as follows: Heteroxanthin ($C_6H_6N_4O_2$), paraxanthin ($C_7H_8N_4O_2$), episarkin ($C_4H_6N_3O$), carnin ($C_7H_8N_4O_3$), and epiguanin ($C_6H_7N_5O$).

These 10 nitrogenous compounds were given the name alloxuric bodies, (*alloxur körper*) by Kossel and Krüger, whereas the last 9 constitute the alloxuric, xanthin or nuclein bases. The term "alloxuric" was applied to them because each was made up of a combination of an alloxan and urea nucleus. Emil Fischer has shown that there is a very intimate relationship between the various members of this group, and has demonstrated the remarkable fact that a number of them can be prepared synthetically. He found that they are all derived from a compound $C_5H_4N_4$, which he termed "purin," having a carbon-nitrogen nucleus, the "purin nucleus," as a basis. Purin, according to Fischer, has the

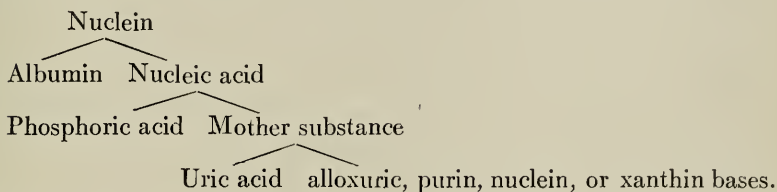


therefrom by the substitution of the various hydrogen atoms by hydroxyl, amide, or alkyl groups. In order to designate the different positions of substitution, Fischer has proposed to number the 9 atoms of the purin



In studying the structural formula of uric acid given above, it will therefore be seen that it is 2.6.8 trioxypurin. Xanthin, accordingly, is 2.6 dioxypurin; hypoxanthin is 6. oxypurin; adenin is 6. amino purin; and guanin is 2. amino-6. oxypurin, etc. To summarize, therefore, the alloxuric or purin bodies include uric acid, together with the alloxuric, purin, nuclein, or xanthin bases. The purin substances are supposed to be contained in the nucleic acid of the cell nuclei in the form of a loosely combined phosphorus-containing body—the nucleotin-phosphoric acid, as Schmiedeberg has termed it.

The close relationship between uric acid and the xanthin or purin bases, and their common origin from nuclein, is shown by the following scheme:



Experimentally, this was clearly shown by Horbaczewski. He found that by adding some oxidizing substance, such as fresh blood, to macerated spleen pulp and then keeping the whole at a constant temperature of 45° C. for several hours, he obtained a certain amount of uric acid. If, on the other hand, no oxidizing agent was added, and only heat applied, he was unable to obtain any uric acid, but secured an identical amount of nuclein or xanthin bases, as indicated by the nitrogen content of each. In other words, it depended upon the facilities afforded for oxidation as to whether the product obtained would be uric acid or the nuclein or xanthin bases.

The feeding of nuclein to man and dogs is followed by a marked increase in the uric-acid output. Horbaczewski, who advanced the erroneous view that uric acid was derived mainly from nuclein of the disintegrated leukocytes, thinks that the increase in the uric acid after nuclein ingestion is not due to the ingested nuclein, but to the nuclein derived from the increased number of leukocytes occasioned by the nuclein administered. An amount of proteid not containing any purin or nuclein bases, but containing an identical quantity of nitrogen in some other form, does not produce a similar rise in the uric-acid excretion, as has been demonstrated by Schmoll and Kaufmann.

The purin bodies from which uric acid is mainly, if not entirely, derived, come from two sources. Burian and Schur have designated them the "exogenous" and "endogenous" purins. The exogenous purins are those introduced with the ingested food, whereas the endogenous purins are those derived from the nucleins of the body and, according to recent investigations, chiefly from muscle metabolism. In the same manner, we speak of "exogenous" and "endogenous" uric acid, when it is derived from these respective sources. By the use of a purin-free diet (such as milk, eggs, butter, cheese, white bread, rice, sago, and fruits) it has been possible to estimate the quantity of nuclein derivatives or purin bodies which arise solely as a result of cellular processes. During the

year 1905, Burian demonstrated that the muscle purins, particularly hypoxanthin, are the chief source of the endogenous uric acid. He finds that muscular exertion is always accompanied by a decided rise in the output of uric acid. The investigations of Burian and Schur show that the endogenous purins excreted in the urine in twenty-four hours vary from 0.10 to 0.20 grams, expressed in terms of nitrogen, of which one-fiftieth to one-tenth is in the form of xanthin or purin bases and the rest as uric acid. On such a diet, Rockwood, working in Chittenden's laboratory, found that the daily output of uric acid in a normal individual ranges between 0.3 and 0.4 grams. He also confirmed the observations of Burian and Schur, that a given individual shows a certain degree of constancy in the daily excretion of uric acid. In other words, the elimination of endogenous uric acid is constant for each individual; that is, it is an individual factor dependent, probably in part, upon the weight of the individual or of the contained organs and tissues. The figures of Burian and Schur given above do not represent the entire amount of nuclein decomposed in the body. The remainder is transformed by specific enzymes of the liver and other organs (to be referred to later) and excreted as urea, or as bodies intermediate between the purin bodies on the one hand and uric acid and urea on the other. Allantoin is one of these intermediate bodies. Wiener holds that glycocoll is the only decomposition product of uric acid. Of the total purin bodies of the urine, nine-tenths is excreted as uric acid and one-tenth as the xanthin or purin bases.

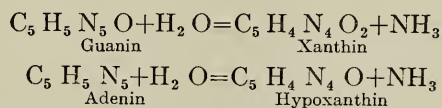
Seat of Formation of Uric Acid.—Until a very recent date, we have possessed no definite knowledge as to the seat of formation of uric acid, nor in what organs the various purin bases were contained or oxidized into higher oxidation products. Garrod, Latham, and Luff, hold that the uric acid is formed in the kidneys. Zaleski, after extirpating the kidneys of snakes, and von Schröder, after removal of these organs in birds, have shown that there is an accumulation of uric acid in the blood and tissues of these animals. This goes to show that the kidneys of birds and snakes, at least, are not the only organs that produce uric acid. Hammarsten claims that we have, up to the present time, no direct proof that uric acid is formed in the kidneys and the general opinion is against the view that uric acid is formed in these organs.

It is probable that uric acid originates in the system only as a result of oxidative processes. Experimentally, the synthetic formation of uric acid has been demonstrated. By passing ammonium lactate through the livers of geese, Kowaleski and Salaskin, in 1901, showed that it was synthesized into uric acid, as indicated by the great increase of the latter in the blood leaving the liver. There is no conclusive evidence, however, that a similar synthetic formation of uric acid occurs in the human subject, although it is possible that it may occur.

Physiologists and physiological chemists have demonstrated that many of the chemical transformations in the body, previously not understood, are really due to the action of specific ferments or enzymes. The very recent investigations of Jones, and his coworkers, Partridge and Winternitz, and of Schittenhelm, have clearly shown us that the various glands and tissues of the body contain specific ferments which are essential for the conversion of one xanthin base into another, and for the conversion of the xanthin bases into uric acid. It has also been ascertained that

certain glands contain only certain ones among the xanthin bases. Jones has found that when such glands as the thymus, suprarenal, spleen, etc., are subjected to autodigestion for several hours at body-temperature in the presence of an antiseptic, definite chemical changes occur. In the case of the thymus, large amounts of xanthin, and a small amount of hypoxanthin, together with uracil, are found in the fluid. With the suprarenal gland, large quantities of xanthin and a small quantity of hypoxanthin, are found. In both of these glands, however, guanin and adenin are entirely lacking. By autodigestion of the spleen, on the other hand, guanin and hypoxanthin are formed abundantly, while adenin and xanthin are wanting. It will be seen that xanthin and hypoxanthin are the chief products of self-digestion of these glands. Quite different results are reached when the glands or their respective nucleoproteids are boiled with acids. When mineral acids are used as the hydrolyzing agent, then the above glandular tissues yield chiefly guanin and adenin. This difference in the result by autolysis and by hydrolysis, with acids, is due to the fact that, in autolysis, the changes are induced by the presence of specific intracellular ferments which possess the power of acting upon certain parts of the purin bodies, transforming them into other related substances.

Jones and Partridge have shown that, in self-digestion of the pancreas in an alkaline medium, large amounts of xanthin and hypoxanthin are found as end products of the autolysis. Guanin and adenin are also formed in all probability, but they are gradually converted into xanthin and hypoxanthin by intracellular enzymes. They found that if pure guanin is placed in a mixture containing finely divided pancreas, with chloroform to prevent putrefaction, and the mixture kept at 40° C. for some time, the guanin is slowly but completely converted into xanthin. The ferment that effects this transformation they have called *guanase*, and it is likewise present in the thymus and adrenals, but is absent from the spleen. Jones and Winternitz have found a similar intracellular enzyme which they term *adenase*, owing to the property it possesses of transforming adenin into hypoxanthin. It is found in the thymus, adrenals, pancreas, and liver. The two ferments are true hydrolyzing agents, the chemical reactions occurring being quite simple and as follows:



It will be noted that there is not only a taking-on of water with the retention of the oxygen, under the influence of the enzyme, but there is also a giving-off of ammonia, by which the change is made possible. As Chittenden has recently stated, these two enzymes are typical deamidizing ferments, destroying the NH_2 group of the adenin and guanin.

Schittenhelm has made the important discovery that it is possible to obtain from simple extracts of the spleen, liver, lungs, and muscles, an oxidizing ferment which is termed *oxidase*, and which possesses the power of transforming the purin bases quantitatively into uric acid. Thus xanthin is converted into uric acid by the mere addition of an atom of oxygen,

and Burian has given to the ferment that brings this about the name of "xanthin oxidase." Schittenhelm failed to find it in the thymus, intestine, kidneys, or blood.

It has for some considerable time been known that the nucleoproteids, nucleins, and nucleic acid, when fed, caused an increased excretion of uric acid, but it has not been heretofore understood how this is brought about. Recent investigations, however, have made this clear. It has been found that certain body cells contain an intracellular enzyme termed *nuclease*, which has the power of liberating the purin bases from their combination as a component part of tissue nucleoproteids. These liberated nuclein bases, such as guanin and adenin, are converted by the deamidizing enzymes, *guanase* and *adenase*, into xanthin and hypoxanthin respectively. Then, by the action of the *oxidase* just referred to, hypoxanthin is oxidized to xanthin, and xanthin to uric acid. It must be emphasized that these enzymes are not distributed indiscriminately throughout the body, but are confined to definite organs or tissues, as has been pointed out. It will thus be seen that we have four distinct enzymes—*nuclease*, *guanase*, *adenase*, and *xanthin oxidase*, or *xanthase*, which are responsible for the production of uric acid in the body. A further observation of great importance is that of Schittenhelm, in which he found that there is another tissue oxidase—contained, so far as is known at present, in the kidneys, liver, muscles, and perhaps, the bone-marrow—which has the power of oxidizing and destroying the uric acid, and converting it into urea and other bodies. This discovery has a direct relationship to the excess of uric acid in the blood in gout; for it is possible to conceive that this excess may be due as well to an inhibition of the action of this uric acid destroying ferment as to an excessive activity of the ferments which lead to the production of uric acid. As pointed out in the section on the predisposing causes for gout, it is possible that alcohol may act injuriously by inhibiting the activity of the uric acid destroying enzyme.

For the above enzymes to perform their functions properly, there must be a proper relationship between the quantity of the purin bodies to be acted on, and the various ferments. Mendel has shown that, if the purin bodies be in excess, their thorough oxidation does not take place, and instead of their being largely oxidized to urea, an intermediate oxidation product—allantoin, is produced, and excreted in the urine in excess.

The exogenous purins we take in our food are either in the form of the free bases adenin, guanin, hypoxanthin, and xanthin, or as combined purins and nucleoproteids. Of the free purin bases in the ordinary food stuffs it is the oxypurins, hypoxanthin, and xanthin, that the body has mainly to deal with, as they are contained in large amounts in meat broths and extracts. They are, however, easily oxidized into uric acid, and excreted as such, or further oxidized into urea or other products by the special oxidase. When combined purins are introduced in the form of nucleins and nucleoproteids, adenin and guanin are liberated by the action of nuclease. The continuance, unchanged, of these two bodies, depends upon the presence and action of the two enzymes, adenase and guanase. If these are present and active in normal degree, we can conceive of a rapid conversion into hypoxanthin and xanthin and then into uric acid. If the enzymes be deficient, then the adenin and guanin will circulate unaltered in the blood, for a time at least. Chittenden offers the suggestion that the pro-

longed circulation of these aminopurins may account for the renal changes in certain diseased conditions, presumably gout; for it has been shown that when adenin is administered to dogs and rabbits, it causes anatomical changes in the tubules of the kidneys, with deposits of spheroliths of uric acid and ammonium urate in the kidney substance.

Since the division of uric acid into the exogenous and endogenous forms, it has been held, until a very recent date, that the endogenous uric acid resulted entirely, or almost entirely, from the nuclein derivatives derived from the destruction of the nuclein of the glandular and tissue cells. In 1905, Burian showed that this view is erroneous. He finds that only a very small amount of the endogenous uric acid has its origin in the nucleoproteids of disintegrating tissue cells or leukocytes, the larger part being derived from the purin-base hypoxanthin, which is continually being formed as a metabolic product of living muscle tissue. It is not possible to go fully into this important observation here. It is sufficient to say that Burian's work opens up a new chapter in purin metabolism, bearing on the production of endogenous uric acid. In the resting state, muscle is continually giving up to the blood a certain amount of uric acid formed at the expense of the hypoxanthin which originates within its own tissue. The oxidation of the hypoxanthin to uric acid is accomplished by the specific oxidase which the muscle itself contains. Burian points out, however, that this oxidase must be so located that the hypoxanthin is converted into uric acid just as it is passing from the muscle fibre into the blood or lymph, since muscle itself never contains any uric acid, only purin bases. He also believes that a certain amount of the uric acid is at once decomposed by the other oxidizing ferment which destroys this acid.

The portion of the endogenous uric acid that results from the disintegration of the nuclei of body cells and leukocytes is also fully believed to be the result of the action of the specific ferments already described. It will thus be seen that these investigations have given an entirely new conception of the seat and method of formation of uric acid in the system. It seems justifiable to hope that this additional knowledge may soon lead to a better understanding of the disturbances of nitrogenous metabolism which appear to lie at the foundation of gout.

Form in Which Uric Acid Circulates in the Blood.—This question requires elucidation. Uric acid is a dibasic acid, and as such may be represented by the formula $H_2(C_5H_2N_4O_3)$. It thus has two atoms of replacable hydrogen. It forms two groups of salts, and according to Bence-Jones and Sir William Roberts, three different salts. For purposes of illustration, sodium may be used as the replacing metal. The salts are as follows: (1) Neutral sodium urate, $Na_2C_5H_2N_4O_3$. (2) Biurates, or acid sodium urate, or sodium biurate, $NaHC_5H_2N_4O_3$. (3) The quadriurates of Roberts, in which the sodium takes the place of one-fourth of the displaceable hydrogen of two molecules of uric acid loosely combined together, such as $NaHC_5H_2N_4O_3, H_2C_5H_2N_4O_3$, the sodium quadriurate.

The neutral urates are purely laboratory compounds, and under no circumstances occur in the human economy. The biurates are not believed to occur physiologically. They constitute the form in which uric acid is deposited about the joints, and in the tophi of gout patients.

Free uric acid never occurs in the blood or tissues, either under physiological or pathological conditions. Sir William Roberts holds that the uric acid circulates in the blood as the loosely combined, readily soluble, quadriurate. While accepted by a number of investigators, this view has met with considerable opposition. Most of the present day physiological chemists claim that there is no such uric acid compound, and that it is impossible for it to exist in a medium such as that of the circulating blood. Opinions differ as to whether it is possible to demonstrate the presence of uric acid or its combinations in the blood of normal individuals. Garrod, Abeles, and Magnus-Levy, claim to have found it in minute traces; Minkowski and Klemperer were unable to demonstrate uric acid in the blood of healthy persons. This diversity in results is thought to be due to the fact that, normally, the uric acid is in loose combination with some other purin product which consequently prevents its precipitation by the usual reagents. Minkowski holds that it is combined with the purin-base, nucleotin-phosphoric acid, and that it is in this form that uric acid circulates in the blood. Others think that it circulates in combination with one of the other pyrimidin derivatives of nuclein, namely, thymic acid.

Daily Excretion of Uric Acid.—The amount of uric acid eliminated daily in the urine by the healthy adult of average weight, when on a mixed diet, ranges between 0.4 and 1.0 grams. Hammarsten gives 0.7 grams as the average. Of the total purin or alloxuric bodies in the urine, nine-tenths exist as uric acid and one-tenth as the purin, alloxuric, xanthin, or nuclein bases. The ratio of uric acid to urea ranges in health between 1 to 50 and 1 to 70, and of uric acid nitrogen to total nitrogen, according to Minkowski, between 1 to 20 and 1 to 120. The form in which uric acid is eliminated in the urine has not been definitely ascertained, but Bunge and, later, Rüdel suggested that it is here also excreted in loose combination with some other organic substance. They hold that this combination is easily broken up, and the uric acid is then set free. It may then either remain free or enter into combination with the sodium, potassium, or ammonium contained in the urine.

(b) *Uric Acid Metabolism in Gout.*—There is undoubtedly marked disturbance of nitrogenous metabolism in gout. The total-nitrogen equilibrium is disturbed. It has been definitely shown by the investigations of Vogel, Schmoll, and others, that a nitrogen retention occurs; that is, that the total nitrogen output is less than the nitrogen intake. Since the adoption of the classification of purins into the "endogenous" and "exogenous" varieties, too little time has elapsed and too few investigations have been published, to draw absolute conclusions as to how the metabolism of each is affected. The studies of Reach, Kaufmann, Vogt, and Chalmers Watson, show that in gout, the exogenous purins are more slowly excreted than in health, and that in some cases there is a distinct retention. Vogt gave rich purin-holding food to a gouty patient and to a healthy individual, and found that in the former there was a delayed excretion, and definite retention of the purin bodies. It can safely be concluded that exogenous purins, in part at least, lead to an excess of the nuclein derivatives in the blood-stream. There is no question but that the metabolism of the endogenous purins is also markedly disturbed in gout. This will probably be best shown by a consideration of the amount of uric acid excreted in

the urine as well as of that present in the circulating blood in this disease.

The Excretion of Uric Acid in Gout.—Garrod was the first to claim that there is a diminished excretion of uric acid in gout. He believed that this was true both of the acute attack as well as of chronic gout. Since the adoption of more reliable methods of quantitative analysis in recent years, Garrod's results have not been confirmed *in toto*. From the analysis of Ebstein, Pfeiffer, Luff, Camerer, Weintrand, Kaufmann and Mohr, Magnus-Levy, His, and others, Minkowski states that the following conclusions may be drawn: (1) The daily excretion of uric acid, in the intervals between acute attacks, ranges within the same limits as does the excretion in healthy individuals. (2) In chronic gout, even in those cases in which there is marked deposition of biurates in the tissues, a constant diminution in excretion of the uric acid has not been definitely proved. (3) Immediately preceding an attack there is regularly a diminution in the amount of uric acid eliminated in the urine, whereas, during and after the attack, the uric acid output is increased.

The writer's analyses, made with Folin's modification of the Hopkins method for estimating uric acid, fully accords with the results stated in Section 3. They, however, differ materially from those given in Section 2 as the uric acid elimination has almost always been below the lower limit for normal, *viz.*, 0.4 grams, in the intervals between the acute attacks in chronic tophaceous gout.

To what are these variations in the uric acid excretion due? Various possibilities present themselves. The diminution in the excretion of uric acid before the onset of an acute attack may be interpreted as meaning either a diminished uric acid production, or a temporary diminished capacity on the part of the kidneys to excrete uric acid. The sudden deposition of uric acid salts about the joints and in the tissues affords a third possible explanation. The increased uric acid output during an attack may be due to an increased uric acid production, or to the possibility that the previously retained uric acid is temporarily excreted in increased quantity. The variations in the excretion may further be explained on the supposition that at times a smaller, and at other times, a larger, part of the uric acid in the organism is metabolized into other waste products, such as urea. It may be possible to draw more definite conclusions as to the cause or causes of these variations in the uric acid elimination in gout after we consider the uric acid content and alkalinity of the blood in this disease.

The Uric Acid in the Blood in Gout.—Practically all observers agree that there is a marked increase of the uric acid in the circulating blood. Garrod first demonstrated this excess by quantitative analysis and, also, by his well-known "thread-test." Klemperer, who was unable to demonstrate uric acid in normal blood, found in three cases of gout 0.067, 0.088, and 0.0915 grams of uric acid in 1000 cc. of blood, during an acute attack. Magnus-Levy made 34 analyses in 17 cases of gout, and found the uric acid to range between 0.021 and 0.10 grams in 1,000 cc. of blood. The same observer also sought to ascertain whether there was any regular difference in the amount of uric acid in the blood during an acute attack and in the intervals. Of 10 cases studied, the uric acid was the same during the acute attack as in the intervals in 5; greater in 2; and less in 3.

It cannot be said then that there is by any means a constant increase in the amount of uric acid in the blood during an acute attack over that present in the intervals.

The Alkalinity of the Blood in Gout.—The methods of determining the degree of alkalinity of the blood are notoriously unreliable. Fokker and others, on the basis of recent work, deny that the blood of the normal individual is alkaline, claiming that it is neutral. However true this may be, Garrod based his theory of the production of gout largely on the belief that the alkalinity of the blood is diminished. He simply makes the statement that the alkalinity of the blood in gout is markedly diminished, and no reference is found in his writings to any quantitative determinations nor any intimation as to how he arrived at this conclusion. Recent investigations along this line, and by methods believed to be reliable, are conflicting in their results. Pfeiffer, Jeffries, and Drouin, claim to have found an increased alkalinity. Klemperer, in 3 cases of acute febrile gout in which the alkalinity was determined by estimating the carbonic acid in the blood—the most reliable method—found a very slight diminution, but not enough to account for the precipitation of the uric acid. In 16 cases in which Löwy's titration method was used, Magnus-Levy found no appreciable diminution in the alkalinity. In 11 cases he compared the degree of alkalinity during and between attacks. In 3 there was a diminution during the attack; in 2, an increase; and in 6, there was no difference. These results in general show that there is no constant diminution in the alkalinity of the blood in gout, nor is the alkalinity apparently diminished to a greater extent during the acute attack than in the intervals.

Klemperer conducted a series of experiments which have a very important bearing on the alkalinity of the blood in healthy and in gouty individuals, as well as on the effect that a possible change in the alkalinity may have on the power of the plasma to hold uric acid in solution. He found that the blood of the gouty person is not a saturated solution of uric acid and that it is still capable of dissolving more of the acid. Whereas, 100 cc. of blood serum from 3 healthy persons was capable of dissolving 0.166, 0.171 and 0.174 grams of uric acid, the same amount of serum from 3 gouty patients was still capable of dissolving 0.126, 0.14, and 0.18 grams of the acid. The conclusion to be drawn from this observation is, that an over-loading of the blood with uric acid is not alone to be regarded as the cause for the deposition of the sodium biurate in the tissues. This is substantiated by the fact that in other diseases, such as leukæmia, there is a marked increase in the uric acid in the blood, yet biurate depositions in the tissues do not usually occur. There are apparently only 5 cases reported in the literature in which definite gouty manifestations have been found in association with leukemia. This number is so small that the co-existence may well be considered accidental.

Origin of the Excess of Uric Acid in the Blood.—Three possibilities present themselves. One can conceive of the increase being due to: (1) Diminished destruction or oxidation; (2) increased formation; (3) diminished excretion by the kidneys.

The evidence on this point has recently been analyzed by Wiener in his excellent review of uric acid in its relationship to gout. He claims that

there is no special evidence to point toward the excess being due to deficient oxidation. Klemperer has shown that the blood of the gouty individual still possesses the power *in vitro* of destroying uric acid, presumably by oxidation. Wiener's analysis was published just previous to the appearance of the recent studies showing the important part that specific ferments play in the formation and destruction of uric acid. As already pointed out, the excess of uric acid in the blood in gout may eventually be shown to be due to a deficiency in the oxidase which normally converts it into urea and other products. The knowledge that there is a special oxidase in the liver, kidneys, muscles and bone-marrow whose function is to further oxidize uric acid to urea and other products, renders it quite possible that the excess of uric acid in the blood may be due to influences which interfere with the oxidizing power of this particular oxidase. The diminished oxidation theory is the one receiving the best support at the present time, and is the one for which the writer thinks there is the most evidence.

Although the increase in the uric acid in the blood and urine in leukæmia and pneumonia is undoubtedly due to increased formation, resulting from increased nuclein destruction, the evidence is not nearly so convincing in the case of gout. We know that uric acid is formed partly by oxidative processes from the nucleins and partly by synthetic formation in the liver. There is no definite evidence of any increased nuclein destruction in gout. There is no leukocytosis, excepting a slight temporary one during the acute febrile attacks; so an increase in the leukocytes with their increased disintegration cannot explain the increase of uric acid in the blood. We have no definite evidence to point toward an increased synthetic formation of uric acid in the liver.

There are some points favoring the view that the excess of uric acid in the blood is due to diminished excretion by the kidneys. In support of it, is the prevalence of, and, according to Levison, the constant association of an interstitial nephritis in gout. Most authorities are inclined to consider the nephritis as a result of the gout. The influence of nephritis on uric acid excretion and its deposition about the joints is shown by Ord and Greenfield's statistics. Out of 96 cases of renal disease there were biurate deposits in the joints in 18. Levison claimed that it was always with contracted kidneys that this deposition occurred. This was supported by the investigations of Luff, who found biurate deposits in the joints in 20 out of 26 cases of chronic interstitial nephritis. These observations tend to show that in interstitial nephritis there is some condition produced, presumably a retention of uric acid, which favors the latter's deposition in the joints. In support of the retention theory may be mentioned the researches of Hans Vogt and Reach, who found that the excretion of uric acid after the ingestion of nuclein or nuclein-containing food is much less marked in the gouty, than in the healthy, individual. Schreiber claims, contrary to Levison's view, that interstitial nephritis is not always present in gout. In these cases without organic renal disease, Minkowski is inclined to support the older view of Garrod that it is possible that a functional disturbance of the kidney may occur which lessens its ability to excrete uric acid. He favors the retention theory as the cause of the excess of uric acid in the blood. He and His have advanced the view that the uric acid, in gouty individuals, circulates in

the blood in a different organic combination from that in which it exists in the blood of healthy persons, and that consequently the kidneys are functionally incapable of eliminating it as in health. A very strong argument against this retention theory is the fact that, even in cases with well-marked nephritis, it is well known that the kidneys are capable of excreting uric acid in quantities considerably above the upper limit for normal for two or three days after the onset of an acute attack.

Taking everything into consideration, the weight of evidence, in the writer's opinion, seems to favor the retention theory as the most plausible view to explain the excess of uric acid in the circulating blood in this disease. Subsequent investigations, however, may show that the excess is due to failure in the action of the special oxidase in the liver and other tissues whose function is to further oxidize uric acid.

Theories of Gout.—Considering the number of these, only the more important ones can be considered and these merely briefly.

Garrod held that in acute gout the alkalinity of the blood is lessened and the uric acid of the blood is increased owing to deficient power of elimination on the part of the kidney. The latter is due, usually, to organic disease but may result from a purely functional disturbance. He attributes the deposition of sodium biurate in the tissue to the diminished alkalinity of the plasma, which is unable to hold the uric acid combination in solution. During an acute paroxysm there is an accumulation of the urates in the blood and the local inflammation is caused by their sudden deposition in crystalline form about the joints.

This theory has had many supporters and in large part can be accepted, but, as we have already seen, any explanation based on the degree of alkalinity of the blood must be received with some skepticism.

Sir William Roberts believed that uric acid normally circulates in the blood in the form of a soluble quadriurate, which may be represented by the formula $\text{NaHC}_5\text{H}_2\text{N}_4\text{O}_3$, $\text{H}_2\text{C}_5\text{H}_2\text{N}_4\text{O}_3$, which is sodium quadriurate. The sodium atom may have its place taken by an atom of any of the univalent metals. In the gouty state, according to Roberts, either from deficient action of the kidneys, or from overproduction of urates, the quadriurate accumulates in the blood. The detained quadriurate, being very unstable and circulating in a medium rich in sodium carbonate, takes up an additional atom of the base, and is converted into the biurate as follows: $2(\text{NaHC}_5\text{H}_2\text{N}_4\text{O}_3, \text{H}_2\text{C}_5\text{H}_2\text{N}_4\text{O}_3) + \text{Na}_2\text{CO}_3 = 4\text{NaHC}_5\text{H}_2\text{N}_4\text{O}_3 + \text{CO}_2 + \text{H}_2\text{O}$. The biurate is very insoluble and less easily excreted by the kidneys. It consequently accumulates in the blood, and exists first in a gelatinous, and later in the almost insoluble, crystalline form. It is then that precipitation is imminent or actually takes place. This is apt to occur where the circulation is poor and the temperature low, and in regions in which the lymph contains a relatively high percentage of sodium chloride, as in the synovial sheaths.

This theory has met with opposition from various quarters and particularly on the part of Tunncliffe and Rosenheim. Minkowski also holds that it is impossible for uric acid to circulate, even in normal blood, as the quadriurate, for in a medium so rich in carbonates and phosphates as is the blood, the quadriurate must necessarily be rapidly converted into the biurate. Minkowski thinks that uric acid normally circulates in the blood in organic combination with nucleotin-phosphoric acid. Others

believe that it is in combination with thymic acid, one of the nuclein derivatives.

Ebstein holds that the local manifestations of gout are due to nutritive tissue disturbances which lead to necrosis. He found, after a study of many of the affected tissues in gout, that one change is common to them all, independently of the urate crystallization, and that is, a necrosis of the parts in which such deposition takes place. He believes that this necrosis is primary, and that it is as characteristic as the biurate deposit. Both changes must co-exist in any tissue in order to constitute a true gouty lesion, and he has found such lesions in the kidneys, in hyaline and fibrocartilage, and in tendons and connective tissue. He calls attention to the early stages of the necrotic process, in which he finds no deposition of the biurates, and consequently maintains that a nutritive tissue disturbance is the primary factor, and uratic deposition a secondary one, in the gouty process, the latter not occurring until death of the tissue takes place. Von Noorden supports Ebstein's views, and believes that the tissue necrosis is due to the action of a special ferment.

In 1784, Cullen advanced the theory that gout was primarily due to an affection of the nervous system. According to this view there is a basic arthritic stock—a diathetic habit, of which gout and rheumatism are two distinct branches. The chief advocate of the nervous theory at the present day is Sir Dyce Duckworth, who at first held that disease of a special tract in the cord was the cause of the tissue lesions in gout. Although he no longer insists that gout is due to a lesion of any particular column of the cord, he just as strongly insists that it is essentially of nervous origin. The influence of depressing conditions, mental and physical, in precipitating an attack of gout, points strongly to the part played by the nervous system in the etiology of the disease. The nervous theory has not received very general support.

In recent years attention has been attracted to the xanthin or purin bases as a possible cause of gout. Kolisch found that although the uric acid excretion is diminished, yet the total output of the alloxuric or purin bodies was increased. He believed that the xanthin bases normally are finally oxidized into uric acid in the kidneys, but that in gout the kidneys are diseased, and their power to oxidize the xanthin bases is consequently impaired. His results were obtained by methods shown later to be inaccurate, and Sülzer, Laquer, and Magnus-Levy, failed to confirm them. Whatever part the xanthin bases may subsequently be shown to play in the etiology of gout, up to the present they have not been shown to exert an important influence. Undoubtedly some of the xanthin bases are definitely toxic. Kolisch and Croftan have produced arterial and renal lesions by injecting hypoxanthin into animals. I. Walker Hall confirmed these results and also produced parenchymatous changes in the liver by long continued injections of hypoxanthin. Taylor has already in Chapter XIV considered gout from the standpoint of an auto-intoxication.

It has been claimed by some that glycocoll is found quite frequently in the urine of gout patients, and it has been thought that it may be a factor in the causation of the disease. As yet, too little is known to express any definite opinion on this point. Its relationship to uric acid is well known. On heating the latter with concentrated mineral acids in sealed tubes to 170° C., it splits up into glycocoll, carbon dioxide, and ammonia.

Summary of Our Knowledge Concerning the Chemistry of Gout.—It will be seen from the foregoing that there is much divergence of opinion regarding the true cause of gout. The subject still awaits a definite elucidation. Whatever may eventually be determined to be the actual cause of the disease, there is a growing impression that uric acid plays only a secondary part, and I. Walker Hall, who has been one of the most active students of the disease, recently asserted that it is in no way an etiological factor. On one point all investigators agree, and that is that there is marked increase in the uric acid circulating in the blood. The writer's conviction is that the weight of evidence is in favor of this increase being due to diminished oxidation or destruction of uric acid in the system. There is general agreement that there is always a retention of uric acid just before an acute attack, and although investigations vary in the results obtained, a marked diminution in the uric acid excretion throughout the entire period between acute attacks in chronic tophaceous gout has constantly been found by the writer. The deposition of biurates in the tissues and about the joints appears to be due to some factor other than the mere presence of an excess of uric acid in the blood. Whether or not a primary tissue necrosis is a necessary antecedent to the biurate deposition, as Ebstein claims, still lacks definite proof. There is no positive evidence that there is a greater excess of uric acid in the blood during an acute exacerbation of the disease than in the intervals. In the light of recent investigations on the alkalinity of the blood in gout, it seems impossible to attribute the deposition of biurates to diminished power of the blood to hold the uric acid in solution, owing to the diminished alkalinity of the serum, as claimed by Garrod, Haig, and others.

Considering the fact that recent investigations have shown that the hyperglycemia of diabetes is probably due to the absence of certain sugar-destroying ferments or bodies, and accepting the view that the excess of uric acid in the blood in gout is due to deficient oxidation, it seems quite possible, in the light of recent studies, that this excess may be due to the deficiency of a special tissue enzyme. The work of Jones, Schittenhelm, Burian and others, has shown that certain of the glandular organs produce the ferments guanase, adenase, and oxidase, which oxidize guanin, adenin, and hypoxanthin into xanthin, hypoxanthin, and xanthin, respectively. Another oxidase oxidizes xanthin into uric acid. It is quite probable that somewhere in the body, a ferment is produced which, normally, is necessary for the proper destruction or oxidation of uric acid, and that owing to some organ or organs failing to produce this ferment, proper oxidation of uric acid does not occur and the latter consequently accumulates in the blood in excess. The studies of Schittenhelm add considerable support to this hypothesis. This observer has shown, as we have seen, that the liver, kidneys, muscles, and bone-marrow contain a special oxidase which possesses the power of oxidizing and destroying uric acid and converting it into urea and other products. We can conceive how certain factors, one of which is believed to be alcohol, could inhibit the action of this ferment, thus leading to diminished destruction of uric acid and its consequent increase in the circulating blood.

While the arthritic manifestations of gout are usually explained as being due to the mechanical irritation of the biurates locally deposited,

the uric acid theory does not so satisfactorily explain the nervous and visceral manifestations of the disease. There are many who oppose this view as to the cause of the joint pains in acute attacks. No other satisfactory explanation has been advanced. It seems more probable to the writer that the pain is actually due to the acute inflammation which occurs, with stretching of the peri-articular tissues and consequent irritation of the surrounding nerves. We have no positive indication that uric acid itself is definitely toxic in the sense in which we use the term to designate a chemical poison. Animals have been made to ingest large quantities of uric acid with their food, and urates in solution have been freely injected into their veins, without causing any signs of poisoning. It may be that some other toxic agent is responsible for the symptoms of irregular gout. Roberts thinks, however, that even in this form, the symptoms may be due to the actual deposition of sodium biurate in the fibrous tissues in and about the nervous system and in the gastrointestinal tract. He suggests that the failure to microscopically demonstrate such deposition may be due to insufficient search or to the possibility of the biurates subsequently disappearing.

Pathology.—The Blood.—There is always an excess of uric acid as was first demonstrated quantitatively by Garrod, in 1848. He found 0.025 to 0.175 grains of uric acid in 1,000 grains of serum. Klemperer found as high as 0.00915 grams in 100 cc. of blood, and, in 17 cases, Magnus-Levy found the amount to range between 0.0021 and 0.010 grams in the same quantity of blood. The excess of the uric acid is also demonstrable by Garrod's well-known thread experiment, which may be performed either with the separated serum of the drawn blood or with serum obtained by the application of a blister. To 2 drams of the serum, in a rather flat watch crystal, add 6 minims of moderately strong acetic acid for each fluid dram used. Mix well, and introduce one or two ultimate fibers from a linen thread or from a piece of unwashed linen fabric. Set aside in a cool place for from thirty-six to sixty hours until the serum is quite set and almost dry. If uric acid be present in excess (equal to at least 0.025 grains of uric acid in 1,000 grains of serum in addition to the trace existing in health) it will crystallize out on the fibers and, under the microscope, will resemble the appearance of sugar-candy on a string.

There is no special tendency to the development of anæmia. The leukocytes are not increased except slightly during an acute attack. One of our hospital cases with tophaceous gout eventually died of pernicious anæmia with a perfectly characteristic blood-picture. Neusser occasionally found that there is an eosinophilia and Chalmers Watson has seen numerous degenerated myelocytes during acute attacks. Neusser's so-called "perinuclear basophilic granules," which he considered pathognomonic of a uric acid diathesis, have been shown by the writer and others to be due to artifacts and to occur in the blood of normal individuals with the same technique. It was also shown that there was no association between the excretion of the alloxuric bodies and the relative abundance of these granules, as he supposed. Recent investigations tend to show that there is no constant reduction in the alkalinity as has been held by Garrod, Haig, and others. In the cases of saturnine gout, the red cells are likely to manifest the basophilic granular degeneration seen in lead poisoning.

The Joint Changes.—The characteristic lesions of gout manifest themselves particularly in and about the articulations. They are dependent upon the deposition of uric acid in the form of sodium biurate, and on the inflammatory and degenerative processes which result therefrom.

On examining a gout joint at autopsy, the articular surfaces will be found studded with specks, streaks, or patches of white, mortar-like material. This is composed of sodium biurate deposited as long acicular crystals. It is likely to be most abundant toward the central portion of the articular surfaces. Close examination will show that the sodium biurate is not on the surface of the cartilages but that it is covered over by a thin layer of cartilaginous tissue. It seldom reaches the bone and, as Garrod pointed out, rarely penetrates beyond two-thirds of the depth of the cartilage. In very advanced, chronic cases there may be actual erosion of the cartilage, but this is rare as compared with arthritis deformans. In the chronic cases, the biurate deposit often invades the capsular tissues, and may even infiltrate the skin, and lead to suppuration of a joint tophus. The biurate deposit in the cartilage can be demonstrated microscopically by examining sections cut at right angles to the articular surface; also by the simpler method of scraping off some of the articular cartilage and teasing in salt solution and examining microscopically. It is believed that the biurate is deposited from the synovial fluid of the joint cavity. In the chronic cases there is much thickening of the capsular tissues. In these there may be increased dryness of the joint; but if the patient dies during an acute attack, there is usually, particularly in the knee-joints, an excess of synovial fluid, and the synovial membrane may be reddened and injected. The synovial fluid is usually somewhat turbid, and contains a varying number of polymorphonuclear leukocytes and occasionally acicular crystals of sodium biurate.

There is considerable diversity of opinion, regarding the essential cause of the biurate deposition. Ebstein insists that there is always a primary tissue-necrosis. It seems more likely that, if this view be correct, the areas of necrosis result from the toxic action of some as yet unknown poison, or to one of the intermediate purin bodies. No matter in what part of the body the biurates are deposited, he claims that the tissue-necrosis is the primary factor. These necrotic areas are most liable to occur in the joint cartilages and other cartilaginous and articular structures in which the normal nutritional currents are slow. In support of his view, he states that he has often found areas in which there was necrosis without biurate deposition. In these areas of coagulation necrosis, the reaction is always acid, so that the conditions are favorable for the precipitation of the uric acid in the form of the crystalline biurate. As has been stated, von Noorden thinks this necrosis may be due to a special ferment. His and Mordhorst claim that the deposition of the sodium biurate is primary, and that the tissue necrosis is a secondary process. According to Roberts, the biurates are deposited most abundantly in cartilaginous tissue, because here the temperature is lowest, the circulation poorest, and, in the case of the articular cartilage, it is bathed with the synovial fluid which is rich in sodium chloride, and which he claims favors the deposition of sodium biurate. According to Wynne, the marginal outgrowths about the gouty joints are true exostoses. The bursæ may be acutely inflamed and may contain deposits of biurate of soda.

The frequency with which biurate deposits are found in the joints at autopsy corresponds closely with the relative frequency with which the gouty arthritis is seen clinically. Norman Moore has brought this out well in an analysis of 80 autopsies on gout patients. The joints most commonly involved are the metatarso-phalangeal joints of the big toes, and frequently these are the only ones affected. Then follow the tarsal joints, ankles, knees, hands, and wrists. The elbows, shoulders, and hips, are more rarely involved. Among the rarest sites of uratic deposits are the articulations of the jaws, larynx, and sternoclavicular joints.

Situations in Which Tophi Occur.—Biurate deposits occur in other situations than in the joints and their neighborhoods. These are termed “tophi,” a name derived from the Hebrew, and signifying “concretions.” They are also known as “chalk-stones.” The commonest situation for them to occur in is on the helix or anti-helix of the ear. They are also frequently found in the tendons and aponeuroses. In one case the writer saw a tophus measuring 3 by 6 cm., in the tendo Achillis. They are not infrequently seen in the subcutaneous tissue. The commonest seats of skin tophi are the extensor surfaces of the fore-arms, near the elbow-joint, and the neighborhood of the patella. They may be mistaken for the subcutaneous fibroid nodules of rheumatism. The writer has observed a patient with numerous tophi in the prepuce; another had a large group of them over the sacrum. They may also occur in the palms and soles, nose, and tarsal cartilages of the eyes. Less common situations for biurate deposits are the laryngeal cartilages, vocal cords, cranial and spinal dura mater, the pia mater, sclerotic coat of the eye, the fibrous sheathes of the nerve trunks, and the aortic valves. Enormous tophi, which may break down and suppurate, not infrequently occur about the finger and knuckle-joints. Ebstein and Sprague have carefully analyzed the tophi, and find that they contain, on an average, 57 per cent. of sodium biurate, and from 12 to 13 per cent. of calcium biurate. Somewhat similar to these tophi in man, are the deposits characterizing “guanin gout” in hogs. When these animals are fed in a certain way, one sees in the muscles, ligaments, and articular tissues, small whitish deposits which are made up of guanin. These are frequently seen in Smithfield and Westphalian hams.

The Kidneys.—Of the visceral lesions in gout, those of the kidneys are the most frequent and important. Nephritis is extremely common, and, according to Levison, is always present. Ebstein has described two types of gout cases: First, the “primary renal gout”; and second, the “primary articular gout.” In the former, the renal disease has existed for some time, and, subsequently, articular manifestations of gout appear. Such a case recently occurred in a colored man, aged twenty-four years, admitted to the Johns Hopkins Hospital. For several months he had complained of the usual symptoms of chronic nephritis. There had been no previous arthritic history. A few days before his death, he developed pain and swelling of his right big toe-joint. This joint at autopsy showed the characteristic deposits of sodium biurate in the articular cartilage. The kidneys were much contracted. In the latter type, the articular manifestations antedate the onset of the clinical symptoms of nephritis. The form of nephritis usually met with in gout, is that characterized by granular degeneration and marked atrophy. It is often spoken of as the “gouty kidney.”

On the other hand, the arteriosclerotic kidney may be met with. Here the kidney is larger, beefy, red, and very hard. There appears to be no special difference between the kidney of saturnine and that of ordinary gout. The gouty kidney, on section, not infrequently shows white deposits of sodium biurate. In the cortical substance the deposit is scanty and occurs in specks scattered irregularly through the tissue. It is, however, most frequently seen, and most abundant, in the pyramids, occurring in streaks running in the direction of the tubules, particularly toward the apices of the pyramids. In both situations, the deposit is usually situated in the intertubular tissue, but it may also occur, as Virchow, Wagner, and Lancereaux have shown, in the lumina of the tubules. When examined microscopically, it is seen to exist as acicular crystals, just as in the gouty joints. These deposits were first described by Castelnau. They are not so frequently found as we would be at first led to infer. Norman Moore found them in only 12 out of 80 cases. Elstein holds that a tissue necrosis antedates the biurate deposition. Aschoff and Minkowski, on the other hand, claim that they have found the crystals extending from the periphery of the deposits into the surrounding healthy renal tissue, which showed no indications of necrosis. Osler holds that these deposits must not, however, be always interpreted as meaning that the individual has gout, as they occasionally occur without the person having had any gouty manifestations.

Cardiovascular Lesions.—Arteriosclerosis is very common. Nearly all cases of chronic gout show marked thickening of the peripheral arteries. Whether the arterial thickening is due to the toxic action of the excess of uric acid in the blood, to that of the products of intermediary metabolism, or to the contributory factors producing the gout—*viz.*, alcohol, lead, or excessive food, is difficult to determine.

The combination of nephritis and arteriosclerosis with consequent increased arterial tension, frequently leads to hypertrophy of the left ventricle. The arch of the aorta is frequently involved in the arteriosclerotic process. The orifices of the coronaries may be narrowed, and the coronary vessels themselves sclerosed. The coronary involvement renders the subject liable to attacks of angina pectoris. For the same reason, myocardial changes are common, and death may result from failure of compensation. Fatty degeneration of the heart muscle occurs. A gouty pericarditis is not uncommon. In rare instances, sodium biurate deposits have been found in the aortic valves.

Respiratory System.—Sodium biurate deposits may occur in the vocal cords, and in the epiglottis and laryngeal cartilages. In rare instances the biurate crystals have been found in the sputum. Emphysema is very common in chronic gout, and the lungs may show a chronic bronchitis at autopsy.

Symptoms.—Acute Gout.—In the initial attack there may be no premonitory symptoms. A previously healthy man of middle age retires feeling perfectly well. During the night he is awakened with intense pain, usually in the right metatarsophalangeal joint. By morning the joint is reddened, slightly swollen, and sensitive to the touch. The temperature is moderately elevated, reaching usually to between 101° and 103° F. As morning approaches, the pain, which has been agonizing and makes the patient feel as though the joint is being squeezed in a vise, gradually sub-

sides, and, beyond having a feeling of general malaise and of anorexia, he experiences a fairly comfortable day. The next night the attack recurs, and the pain, as Sydenham says, "insinuates itself with the most exquisite cruelty among the numerous small bones of the tarsus and metatarsus, in the ligaments of which it is lurking." There is a repetition of these attacks each night for a week or ten days, constituting a so-called "fit of the gout." For the first few days the swelling of the joint increases, coincident with which there is a gradual abatement of the intensity of the pain. The skin over the joint is reddened and shiny. The surrounding veins are slightly dilated, and, toward the end of the attack, there may be slight pitting on pressure over the joint. The inflammation never goes on to suppuration. With the subsidence of the acute swelling, the skin may desquamate. During the acute febrile period, there is a leukocytosis which may reach 20,000 per cmm. In the initial seizure both big toe-joints may be involved. On the other hand, these articulations may escape, and the tarsal and tarsometatarsal joints may be first affected. In these instances the "fit" generally lasts considerably longer. After the attack, the general health may be decidedly improved. There may be no recurrence of the acute attack for years, or even decades. More commonly, however, only months elapse, and there is a tendency to periodical recurrences in the spring and fall. Premonitory symptoms occasionally precede the acute attacks for a number of days, and the victim can often predict its onset. These symptoms are quite diverse. The most prominent ones are digestive disturbances—loss of appetite, flatulence, and acidity. Nocturnal restlessness, irritability of temper, and depression of spirits may also occur.

Chronic Gout.—With the progress of the disease, the acute exacerbations become more frequent and a larger number of joints become affected. The tarsal-, ankle-, knee-, hand-, and wrist-joints are the ones most likely to be involved, in the order of frequency mentioned. The elbows, shoulders, and hips, are more rarely attacked. Each acute attack is supposed to be occasioned by the sudden precipitation of the sodium biurate in and about the joints. The periarticular tissues become thickened, and densely infiltrated with biurates. The latter, particularly about the toe-, knee-, finger-, and elbow-joints may give rise to large joint-tophi, which, in the case of the knee- and elbow-joints, may reach the size of a walnut. These tophi may cause striking knob-like deformities of the knuckle and interphalangeal articulations. They gradually become superficial, and appear whitish through the superimposed skin. The latter, especially over the knuckle and metatarsophalangeal joints, may become inflamed and actually ulcerate, and the contents of the tophi discharge as a whitish, chalky material, which, on microscopic examination, reveals the characteristic needle-shaped crystals of sodium biurate. In these cases of chronic "tophaceous" gout, the commonest situation for the tophi is the cartilage of the ear, in the region of the helix and antihelix. They appear first as slight reddish elevations in which, as time goes on, the biurate can be recognized with the naked eye as a whitish "chalk-stone like" deposit. The term "chalk-stone" is not altogether a misnomer, for Ebstein and Sprague have shown that tophi contain from 12 to 13 per cent. of calcium biurate, although the greater portion, 57 per cent., is composed of sodium biurate. Subcutaneous tophi may occur about the knees and along the

extensor surfaces of the forearms, and may be mistaken for rheumatic fibroid nodules. They may also occur in the palms, and soles, and over the sacrum, and in the tendo Achilles. Tophi sometimes occur in the tarsal cartilages of the eye, in the sclerotics, and in the cartilage of the nose. The bursæ over the olecranon and patella may become inflamed and be the seat of sodium biurate deposition. Polyarticular attacks, with moderate fever reaching 101° F. occur with frequency, and in the intervals the unfortunate victim is not entirely free from pain, and always conscious of joint disability. Owing to the lessened amount of synovial fluid in these chronic cases, audible creaking of the joints may occur, and there is sometimes palpable crepitation. The acute joint exacerbations may be afebrile, a feature which should always lead the physician to suspect a gouty origin for the joint symptoms. The pulse tension is increased, the peripheral arteries become sclerosed, and hypertrophy of the left ventricle develops. The urinary changes are those of a chronic interstitial nephritis and will be referred to later. Cramps of the calf, abdominal, and thoracic muscles, may be most annoying. Digestive disturbances are common. The victim of chronic gout may possess marked mental and bodily vigor. Certain of the most distinguished members of our profession have been martyrs to the disease, notably the older Scaliger, Jerome Cardan, and Sydenham, whose statement that "more wise men than fools are victims of the affection" still holds good. Although the subject of chronic gout is liable to be carried off by some terminal affection such as uræmia, pleurisy, pericarditis, peritonitis, and meningitis, yet the victims not infrequently live to a good old age. The question has been much discussed as to whether Heberden's nodes ever occur in gout. Although of rare occurrence, it seems quite certain that they do occur, for Charcot, Duckworth, and Minkowski, have described them in cases of unquestioned gout. Dupuytren's contraction of the palmar fascia has been described.

Irregular Gout.—This comprises a nondescript group of symptoms which have usually been embraced under the terms *lithæmia*, or a *uric acid*, *lithic acid*, or *gouty diathesis*. These irregular features are observed in members of gouty families who may never have suffered from an attack of gouty arthritis. They occur, also, in those who have eaten and drunk too freely, without taking sufficient exercise, and who have been fortunate enough to escape an acute attack. In families with marked hereditary predisposition, the daughters often escape, while one son may have gouty attacks of great severity even though he lives a temperate life and endeavors to avoid the conditions favoring the disorder. Another son, on the other hand, has only the irregular features, and never the acute articular affection. While the irregular manifestations are more likely to occur in inherited gout, they may also occur in the acquired form. There is an unfortunate tendency on the part of many physicians to ascribe certain obscure symptoms to a so-called uric acid diathesis, especially if they find a deposit of uric acid or urates in the urine, although there is often not a vestige of evidence to justify this view. There are certain health resorts in this country from which nearly every patient comes away imbued with the firm conviction that his blood is "filled with uric acid," and that this is responsible for his various nervous features. The patients are usually pleased with the explanation, and it is a difficult task to dis-

abuse their minds of the fallacy. Among the commonest manifestations of irregular gout are the following:

(a) *Cutaneous Eruptions*.—The most distinctive is eczema. The favorite seat is the external ear, but the inflammation may spread to the face, forehead, and back of the neck. It may be very obstinate, and even extend to other parts of the body in patients of advanced years. Symmetrical patches of psoriasis may occur on the legs. Attacks of herpes zoster have occasionally occurred. The nails are often striated and fluted, or lined vertically. The French have written extensively on the skin manifestations of irregular gout, and speak of them as the *arthritides*.

(b) *Alimentary Disorders*.—There may be psoriasis of the tongue. Notwithstanding numerous statements to the contrary, Duckworth asserts that no uratic deposits are met with in connection with the jaws, teeth, or gums. It has been held by some that the development of tartar on the teeth is a gouty manifestation. There seems no justification for this view. Some cases are subject to frequently recurring attacks of pharyngitis with great injection of the vessels. A gouty parotitis occasionally occurs. Attacks of what is termed biliousness, in which the tongue is furred, the breath foul, the bowels constipated, and the action of the liver torpid, are not uncommon in gouty persons.

(c) *Nervous Manifestations*.—Some of the most frequent manifestations of irregular gout come under this heading. Headaches and migraine attacks are common. Haig has laid special stress on these symptoms, and he thinks that they are due to an excess of uric acid. Neuralgias are not uncommon. Sciatica is believed frequently to have a gouty basis. Duckworth has emphasized the occurrence of hot or itching feet at night. Plutarch mentions that Strabo called this symptom "the lisping of the gout." Cramps in the leg and abdominal muscles may be troublesome.

(d) *Urinary Disturbances*.—Many fallacious opinions have been formed by physicians concluding that a person is suffering from a uric acid diathesis, by finding deposits of uric acid and urates in the urine. The solubility of the latter is dependent upon so many factors, important among them being the amount of urinary pigment and the percentage of the various salts, that it is entirely unjustifiable to draw any definite conclusions as to the quantity of uric acid excreted without making actual quantitative analyses. Uric acid precipitation may occur, although there may be actual diminution in the uric acid excretion in the twenty-four hours. Individuals with a gouty habit are undoubtedly prone to gravel, and to uric acid calculi. Duckworth points out that articular gout and calculi rarely co-exist, although they may alternate. Albuminuria is very common in the gouty dyscrasia. Oxaluria also occurs. Hematuria may occur in very old persons. Phosphatic gout has been described. It occurs without the articular features. Severe pain comes on in the night, and there is spasmodic dysuria. Urethritis, with a purulent discharge, is said to occur either spontaneously or following a pure connection.

(e) *Ocular Manifestations*.—Hutchinson has called attention to hot and itching eye-balls as a frequent sign of masked gout. Associated or alternating with this symptom there may be attacks of episcleral congestion. The writer observed repeated attacks of unilateral conjunctivitis in a gouty patient, who for years had not had any articular symptoms. These would occur together with, or independently of, a gouty pharyngitis.

(f) *Cardiac Manifestations*.—A peculiar paroxysmal disturbance of the circulation is sometimes witnessed, in which the heart-beats are very rapid and a condition is produced which Roberts terms the “runaway heart.” There may be attacks of false angina pectoris, in which there are no manifestations of cardiac disease.

(g) *Pulmonary Features*.—Greenhow has pointed out that persons of the gouty habit are liable to suffer from chronic bronchitis. Asthmatic paroxysms may also occur. The prevalence of emphysema is well recognized.

The Urine in Gout.—During the acute paroxysms the urine is scanty, high colored, and is generally stated to contain a deposit either of urates or uric acid. In the writer’s experience in hospital work, such a deposit is the exception rather than the rule. There is usually a trace of albumin, and there may be a mild glycosuria. Careful search will usually show a few hyaline or granular casts. Quantitative analyses will always show a marked reduction in the amount of uric acid below the usual level for two or three days before the acute attack. Twenty-four or forty-eight hours after the onset of the acute symptoms, the uric acid curve rises, and the amount may reach 0.7 to 1.0 gram, the upper limit for normal. As the acute symptoms subside, the curve falls to 0.4 gram, the lower limit for normal, or usually below this. In chronic gout, the urine is usually increased in quantity, pale, of low specific gravity, and always contains traces of albumin and hyaline and granular casts. Although some have failed to find a constant reduction of uric acid in the intervals between the acute attacks in these cases, the writer’s analyses have practically always shown a very marked reduction, often not more than 0.1 or 0.2 gram being precipitated in the twenty-four hours. In one or two cases, he has failed to find, on certain days, any precipitation of uric acid as ammonium urate, with Folin’s modification of the Hopkins quantitative method. Many hold that there is no corresponding increase in the excretion of the phosphoric acid with that of the uric acid during the acute attack, but, in some of the cases followed, the writer found a striking parallelism in the curves of the two acids. If the uric acid be derived from nuclein destruction a correspondence in the curves would rather be expected.

Complications.—**Cardiovascular.**—Arteriosclerosis is extremely common and is always found at autopsy in the chronic cases. Owing to the increased tension, hypertrophy of the left ventricle occurs. In due time this may give way to dilatation, causing palpitation, irregular heart action, and eventually a condition of asystole. Myocarditis is very common in the obese cases. This is probably induced by the atheroma involving the coronary arteries, and may be the eventual cause of the patient’s death. Owing to the coronary disease, true anginal attacks may occur. A terminal pericarditis is not an uncommon event, but this is usually attributed to the renal lesion rather than directly to the gout itself. Aneurism and apoplexy may occur.

Phlebitis and venous thrombosis are well recognized as occasionally of gouty origin. The French are inclined to the view that many instances of so-called idiopathic thrombosis of the veins are due to a gouty dyscrasia.

Renal.—A chronic interstitial nephritis, and small granular kidneys, are almost invariably present in the chronic form of the disease, and the majority of gout patients die of uræmia.

Retrocedent Gout.—This term is applied to a group of serious internal symptoms, occurring coincidently with a rapid disappearance, or improvement, of the joint manifestations. They may be so grave as to cause death, and may be considered among the complications of the disease. With a sudden cessation of the joint inflammation there may be severe gastro-intestinal symptoms—pain, vomiting, diarrhœa, and great depression, and death may occur during such an attack. On the other hand there may be cardiac manifestations—dyspnœa, precordial pain, and irregular heart action. Cerebral features, such as delirium, coma, or apoplexy, may occur, but in a majority of cases these symptoms are probably uræmic.

Of the *eye* complications, an iritis is recognized as being of gouty origin. Glaucoma occurs. Hutchinson has described a hemorrhagic retinitis. This may be of renal origin, but it is especially characterized by being unilateral, and affecting the left eye most frequently. A suppurative panophthalmitis has also been described.

Glycosuria and Diabetes.—Glycosuria is comparatively common in gout. It may, in certain cases, be dignified by the name of mild diabetes mellitus. It occurs, usually, in the obese gout patients. The glycosuria may alternate with arthritic manifestations (*diabetes alternans*). Lecorché observed 23 cases of transitory or permanent glycosuria in 150 cases of gout. The etiology of the glycosuria is difficult to explain, but Minkowski thinks that, owing to the prevalence of arteriosclerosis in gout, there may be sclerotic changes in the pancreas, as a result of the arterial disease, corresponding to the arteriosclerotic diabetes described by Fleiner, Hoppe-Seyler, and others.

Diagnosis.—In the majority of cases of the acute form of the disease, no great difficulty should arise. The predilection for the local inflammation to attack the metatarsophalangeal and the tarsal joints is very characteristic. The marked reddening, and the shiny appearance of the skin, together with the intensity of the pain, is extremely suggestive. Before the disease has definitely reached the chronic stage, it must be remembered that the joint inflammation may be polyarticular, and many of these cases are diagnosed as acute rheumatism. Careful inquiry regarding heredity, habits as to eating and drinking, together with the occupation, will often give the proper clue. The examination of the blood for an excess of uric acid is undoubtedly of value. Quantitative determinations are too complicated, and the Garrod thread-test suffices. A positive test practically indicates gout, as the only other conditions in which we meet with an excess of uric acid in the blood are pneumonia and leukæmia, with which there can be no confusion. Unless the uric acid curve can be followed before, during, and after, the subsidence of the acute attack, the writer's own feeling is that the urinary examination gives little aid in making a differential diagnosis.

It is in the chronic form, with occasional acute exacerbations, that the correct nature of the arthritis is often overlooked. This is particularly the case if tophi have not yet appeared; but many cases go begging for a diagnosis even when these are present, owing to the failure of the physician to search regularly for tophi in the ears in all cases of acute or chronic joint affections. The tophi, as we know, are commonest in the cartilaginous portions of the ear in the vicinity of the helix and antihelix. They are

usually small, superficial, and whitish in appearance. They may, however, be more deeply seated and the biurate deposits may not be seen with the naked eye. Microscopic examination of the contents shows the characteristic needle-shaped, acicular crystals of sodium biurate. The presence of these crystals is pathognomonic of gout. Not to be confused with the tophi, are Woolner's tip or the Darwinian tubercle, which is more developed in some of us than in others, small fibroid nodules on the margin of the ear, and small sebaceous cysts. The latter is the only one to give rise to any real confusion, and the finding of oil droplets and epithelial cells, with the absence of biurate crystals in the contents, easily differentiates the two. Where there are large biurate accumulations about the toe-, finger-, knee-, or elbow-joints, the diagnosis of the affection is manifest at first sight. It must be recalled that subcutaneous tophi, clinically indistinguishable from rheumatic fibroid nodules, may occur over the extensor surfaces of the forearms and about the knees, and may, to the uninitiated, be confirmatory of a diagnosis of rheumatism. It is well in any such doubtful cases to excise one of these nodules and examine microscopically. The presence of sodium-biurate deposits in them points definitely to gout. A feature of diagnostic importance is the fact that an attack of acute gouty arthritis may be afebrile. Any polyarthritis, with acute manifestations and unaccompanied by fever, should always cause a strong suspicion that it is gouty in origin. In these chronic cases, the habits of life and the history of the situations of the initial attack of arthritis is most important. If there be an arthritic family history, if the patient has indulged freely in fermented beverages, or has had an occupation subjecting him to possible lead infection, and if the initial or early attacks have been limited to the metatarsophalangeal or tarsal joints, the chances are strongly in favor of the disease being gout. The *x*-ray photograph may be of some assistance. Where there are periarticular deposits of biurates in considerable masses, these will be recognized as shadows in the photograph. Where this is the case one will be reasonably sure, without the photograph, that the periarticular thickening is due to biurate depositions. The weak feature in the diagnostic value of the Röntgen rays, is that they are practically of no assistance just in those cases where they would be of the most value, namely, where the biurate deposits are limited to the articular cartilages. In these cases, the *x*-rays fail to reveal the existence of the deposition, either in the photographic plate or in the reproduction.

As our knowledge of chronic articular affections has increased, the opinion is becoming more firmly established that there is no such condition as chronic articular rheumatism. An acute rheumatic arthritis, when it subsides, practically never leaves any deformity or limitation in functional activity. Consequently, when deformity or impaired motion supervenes upon one or more attacks of acute arthritis, we can be reasonably certain that we are not dealing with a rheumatic affection, but rather with gout or arthritis deformans. It is with the latter affection that the greatest difficulty in the differential diagnosis is likely to occur. In arthritis deformans, however, certain features aid us in the differentiation. In the case of deformities of the hands, there is a greater tendency to ulnar deflection of the fingers. A most important differential point is the almost constant occurrence of atrophy of the dorsal interossei muscles of the hands, producing a depressed appearance over the metacarpal region.

Heberden's nodes point toward arthritis deformans, although, as has been already stated, they have been in rare instances described in cases of undoubted gout. The tendency of the laity, and also of many physicians, is to incorrectly consider these enlargements of the terminal finger-joints as a manifestation of gout. Where the larger joints are involved in arthritis deformans, such as the knee, wrist, or elbow, the deformity is more likely to be of a fusiform shape with considerable muscular atrophy above and below. Needless to say, tophi do not occur in this disease. The *x*-rays are of undoubted value in differentiating the two affections when actual joint deformity has occurred. Osteophytic growths, or atrophy of the ends of the bones and of the joint surfaces, point respectively to the hypertrophic and atrophic forms of arthritis deformans. It should be recalled, however, that Wynne has described bony outgrowths about the joints in gout. The joint distortions of arthritis deformans are very common in women while those of gout are rare. Garrod's uric acid thread-test should be tried, and a positive result would indicate chronic gout. The frequently used term "rheumatic gout" should be abandoned. The disease for which it stands has nothing to do with gout and should be called arthritis deformans.

A chronic arthritis, accompanied by marked arteriosclerosis and a urinary picture of chronic interstitial nephritis, should strongly suggest gout as its origin.

The diagnosis of the irregular forms of gout in which there have been no articular manifestations, often presents great difficulty and is subject to much uncertainty. The existence of a family history of gout is very important in arriving at the basal cause in these cases.

The writer's personal conviction is that gout in this country is much more prevalent than is generally supposed. Many cases of the acute, and particularly of the chronic, form are mistaken for rheumatism, owing to the failure of the physician to ascertain the family history, the patient's habits, the history of the early arthritic attacks, and to search for evidences of tophi in the ears or elsewhere. It is important to enter a protest against the tendency in certain quarters to ascribe nearly every obscure symptom, usually those of nervous or gastric origin, to a gouty diathesis. The idea that migraine attacks, accompanied though they may be by a precipitation of uric acid or urates in the urine, are due to a uric acid dyscrasia, is based on evidence that is far from convincing.

Prognosis.—Once manifestations of gout have made their appearance, they are likely to recur at intervals throughout subsequent life. It occasionally happens, however, that a patient, who in earlier years has been subject to recurring attacks of arthritis, may never show any manifestations after the fiftieth or sixtieth year. This may, in part, be a result of treatment, particularly as regards the habits of living, but it occasionally occurs spontaneously, without the aid of therapeutic measures. It is the later fact that should make us rather conservative in drawing conclusions regarding the effect of any line of treatment. A fatal termination is unusual in the acute stages of the disease, although it may occur from the severity of the symptoms resulting from retrocedent or "metastatic" gout. The duration of life is not likely to be materially shortened, so long as the disease maintains its regular character with distinct arthritic manifestations. Often when these appear to play a much less prominent part in the

gouty picture, visceral complications are likely to arise which may hasten the patient's death. The fatal termination in chronic gout cases is usually due to uræmia, myocarditis with dilatation of the heart, or to pericarditis. As we well know, the victims of regular gout often live to an advanced age.

Treatment.—Until we know with positive certainty the actual basal cause for gout, the treatment of the disease must necessarily be largely empirical. There is, as we have seen, a steadily growing belief that the symptoms of gout are not directly traceable to the action of uric acid. The pathological findings indicate, however, that uric acid and its salts play a conspicuous part in the lesions. We have no positive proof that uric acid in itself is toxic, and investigators are inclined to interpret the excess of uric acid in the blood, and the deposition of sodium biurate in the tissues as secondary manifestations and to be rather the result than the cause of the disease. Just what part the products of intermediary purin metabolism play in the actual etiology remains to be seen. That purin metabolism is markedly disturbed is generally recognized, and its best indication is the constant occurrence of an excess of uric acid in the circulating blood. Subsequent investigations may teach us what influences favor or retard the action of the various purin enzymes which we have previously discussed. The various therapeutic measures we have been accustomed to use in the treatment of gout have been directed mainly toward influencing purin metabolism, and particularly with the object in view of reducing the excess of uric acid in the blood. It is conceivable that this reduction may be brought about in one or more of the following ways: (1) diminishing the formation of uric acid; (2) increasing its elimination; (3) increasing the rapidity of its oxidation in the body; (4) increasing its solubility in the blood and tissue juices.

Prophylaxis in Members of Gouty Families.—In families in which there is a marked history of hereditary gout, something may be done to lessen the liability of individual members to develop active manifestations of the disease. By temperate living, abstaining from alcohol, and eating moderately, the risks are materially diminished. An active outdoor life, with plenty of exercise and regular hours, will do much to keep an inborn tendency to the disease in abeyance.

The treatment of the disease after actual manifestations have made their appearance may be discussed under various headings: Hygienic, dietetic, alkalis and mineral waters, medicinal, local measures, and operative treatment.

Hygienic.—Gout, as we know, prevails chiefly among well-to-do individuals who are not forced to make a livelihood by following occupations requiring even the average amount of physical exercise. Many manifest a tendency to obesity and frequently lead sedentary lives. It is most important, therefore, to encourage in these persons a more active outdoor life requiring physical exercise in moderation. This must not be overdone, and must be confined within the limits of fatigue, for we know that an acute attack may be precipitated by excessive physical exertion. The patient should be encouraged to do a certain amount of walking each day, and a particularly useful exercise is horseback riding, owing to the beneficial effect it has on the intestinal functions. Golf can be highly recommended, as it gets the patient into the open air, is not too violent,

and commands a certain fascination for individuals of all ages. As an adjunct to outdoor exercise, certain indoor gymnastics may be with advantage prescribed, such as the use of dumb-bells, Indian clubs, and the various forms of resistance movements. Massage will increase the muscular tone, stimulate the circulation, and tend to improve the general metabolic functions. The skin functions should be increased by systematic bathing. In the sthenic cases cold-baths may be used, and, where there is a tendency to obesity, with no contra-indications in the way of valvular or myocardial disease, an occasional Turkish bath may be taken with advantage. The bowels should be carefully regulated. The patients should dress warmly, avoid rapid changes in temperature, and be careful not to have the skin suddenly chilled.

Dietetic.—The regulation of the food is undoubtedly a most important factor in the treatment. Meat is the article of diet that has been supposed to possess the most baneful influence, and over which there has been the most discussion. We have had the most diverse advice as to what restrictions in this direction should be made. Wollaston, a century ago, and Haig, of the present day, advise a complete exclusion of the meat and insist on the efficacy of a strict vegetable diet. Armstrong and Wainwright go to the other extreme and recommend the "Salisbury" or exclusive red meat diet. Von Mering and Pfeiffer take an intermediate course and advise against any restriction of the meats, even advising them to be given in moderate excess. This remarkable difference of opinion has been, in large part, due to the fact that the true source of the uric acid was not known until quite recent years. So long as the erroneous view prevailed, that uric acid was a mere antecedent of urea, it was natural that there should be a tendency to restrict the richest nitrogen-containing ingredient of the food. We now know that by far the largest proportion of uric acid is derived from the "endogenous" purins of the body, and a much smaller proportion from the "exogenous" purins of the food. It was also claimed that the red meats and game were especially to be avoided; but recent investigations, by Kaufmann and Mohr, show that there is no greater uric acid output when a person is fed on red and dark meats than when he is given white meats in the same amounts. If the former are in any way more injurious, this is probably referable largely to the fact that they are less easily digested. They are supposed by some to be slightly richer in the extractives belonging to the xanthin series, but investigations have not shown this to be the case. The balance of evidence at the present day is against the exclusion of meats, and in favor of their being allowed in moderate amounts. As many gout patients are excessive meat eaters, it is often advisable, from time to time, to limit the meats to one meal a day.

The proteid foods that are considered particularly injurious, are those rich in cell nuclei and, consequently, containing an abundance of purin bodies. These comprise the thymus (sweet breads), liver, kidney, and brain. Weintraud, Umber, and Rosenfeld, have found that they cause a marked increase in the uric acid excretion, and in the amount of uric acid sediment.

The meat extracts are to be avoided, owing to their richness in nitrogenous extractives and salt. Straus and Eitner found that the uric acid

excretion was increased one to one and a half times after the giving of 50 grams—a very large dose—of Liebig's meat extract.

Fresh fish may be permitted in moderation, but, weight for weight, it has been shown that they cause just as large a uric acid output as do meats. Salt fish should be avoided. Fish roe and caviar should be forbidden, owing to their richness in nuclein, although in the latter it is in the form of paranuclein.

Eggs constitute the most valuable proteid food for gout patients, in that they are free from purin bodies. Milk, for the same reason, is also most useful. There is no scientific basis for the belief by some that cheese should be excluded from the diet. According to the analyses of Rosenfeld and Orgler, casein does not cause an increase in the uric acid excretion. Cheese may therefore be permitted in moderation.

Starchy foods may be freely allowed. An exclusive starch and vegetable diet has its advocates still, but their number is gradually diminishing. Bread, rice, potatoes and other garden vegetables, may form a liberal portion of the dietary. Cucumbers and tomatoes had better be avoided. In Germany, particularly, the vegetable albumins have been more or less extensively used as a proteid food, and as a partial substitute for bread in gout. Of these, aleuronat and roborat have been most extensively used.

Until recent years the prevailing belief had been that fruits were harmful. It was thought that the acids contained in the fruits were injurious. Since the time of Wohler, however, it has been held that the acid combinations in the fruits are oxidized in the system into carbonates and consequently fruit must be considered an alkaline nourishment. The best opinion at the present day favors the free use of fruits. The experience in any individual case is the best teacher in this regard, however, for certain fruits such as bananas and strawberries, particularly the latter, are liable to excite joint pains, and to cause pharyngeal symptoms.

Fats, in the form of butter particularly, may be allowed with freedom; and butter in large quantities has been advocated by Ebstein.

All highly seasoned foods should be forbidden. Pepper, paprika, and mustard, should not be permitted in dressings. Their only injurious effect is through impairment of the digestive functions. Vinegar should be avoided. Sir William Roberts, who maintains that the sodium salts are injurious, in that they diminish the solubility of the urates and favor their deposition, advises strongly against the use of sodium chloride in the food. He recommends potassium chloride as a substitute.

It will be seen from the foregoing that the most diverse views have prevailed concerning the proper diet in gout. No set rules can be laid down. The diet in each individual case must be carefully considered. In general terms it may be said that the proteid foods, particularly those rich in nuclein or purin derivatives, should be limited but not excluded. The general conviction at the present day is that quantity plays a more important part than quality, in gout. This is the conclusion recently arrived at by Minkowski, who has carefully reviewed the subject. The duty of the physician is to see that the patient does not overeat, and to keep his digestive functions in the best possible condition.

The majority of gout patients are better off without any alcoholic beverages. Individual experience soon teaches the victim that his general

health is better and that he is freer from attacks by totally abstaining from alcohol. The fermented beverages are those most liable to occasion a lighting up of the arthritic manifestations. The mere indulgence in a glass of beer or wine not infrequently excites in a few hours, or even minutes, twinges of pain in the joints. When alcohol is indicated, as it sometimes is in the asthenic cases with cardiac symptoms, whisky or brandy may be prescribed and does least harm. On the other hand the richer wines, such as port, sherry, Madeira, champagne, and Burgundy, and strong ales and stout, are very likely to provoke symptoms. In Germany and England, where wine-drinking is commoner than in this country, there is a tendency to rather greater leniency in the use of wine, and the lighter forms, such as the Moselle wines, are permitted in moderation.

There seems no just reason why coffee, tea, and cocoa, should be excluded from the dietary, as has been advised by some. It was held that the purin derivatives they contain—caffeine, adenin, theobromine, and theophyllin—might be a source for increased uric acid formation. Rost, Albanase, and others, have shown that caffeine and theobromine are excreted, in part unchanged, in the urine, and in part they are converted into heteroxanthin, but they have not been shown to be oxidized into uric acid.

The gout patient should be induced to drink freely of water, particularly on an empty stomach early in the morning and before the various meals. There is no positive proof that the drinking of water itself causes any material increase in the uric acid elimination, but experience has proved the beneficial effect of the procedure.

Alkalis and Mineral Waters.—Although alkalis have been very highly recommended on many sides in the treatment of gout, owing to their supposed effect in increasing the alkalinity of the blood and consequently rendering the contained uric acid combinations more soluble and more readily excreted, there has in recent years been a growing skepticism of their efficiency. Freudberg has shown that, in the doses in which they are usually given in gout, it is extremely doubtful whether the alkalinity of the blood is at all increased. A serious fallacy also arises from concluding that, because an alkaline salt increases the solubility of uric acid in a test-tube, it is also going to have the same effect in the circulating blood, where the medium is much more complex and where the uric acid combination is entirely different.

Since Garrod confirmed the observation of Lipowitz that lithium urate was very soluble in water, and, in 1858, first recommended the use of lithium carbonate in the treatment of the disease, the various lithium salts have been held in high favor. Lithium carbonate and lithium citrate, in an effervescent tablet of 5 grains, dissolved in a tumbler of water and administered 4 or 6 times daily, are still popular remedies. Potassium citrate, or carbonate, in 20 to 30 grain doses (gm. 1.3 to 2) 4 times daily, may be given. Roberts and Bain advise strongly against the use of sodium salts, as they claim that they are much less powerful uric acid solvents than the potassium preparations. The urates of soda are also held to be less soluble than those of potash. These various alkalis are undoubtedly beneficial, but it is generally conceded that their salutary action is due rather to the liberal quantities of water with which they are administered than to the effect of the drugs themselves.

Mineral waters have always played an important part in the treatment of gout. All forms may be said to be beneficial, but the good effects are due more to the water than to the contained salts. As Osler says, "Much of the humbuggery of the profession still lingers about mineral waters, more particularly about the so-called lithia waters."

It is a curious fact, notwithstanding that Roberts and others have theoretically demonstrated the injurious influence of sodium chloride on the gouty individual, that it is just those continental springs which contain this salt in the largest quantities to which gout patients flock from all quarters of the world. Roberts points out that an acute attack is often precipitated very soon after a "cure" is begun at one of these springs; and he attributes this to the fact that, owing to the excess of sodium chloride in the blood, the latter becomes surcharged with sodium biurate, which suddenly becomes precipitated in and about the joints, setting up an acute attack. Curiously enough, such an explosion is usually followed by a period of much improved health. This Roberts attributes to the temporary freeing of the circulation of the excess of uric acid. The springs that contain the alkaline carbonates and alkaline sulphates are also in repute, and their beneficial action is in large part due to the salutary effects of these salts on the digestion.

The mineral springs best suited for gouty patients in this country are those of Saratoga, Bedford, and White Sulphur; in England, Buxton, Bath, and Strathpeffer; in France, Aix-les-Bains and Contrexéville; in Germany, the Sauerling spring of Carlsbad, Wildbad, and Hamburg. The drinking of water at home in large quantities, and on an empty stomach, is beneficial but not so much so as at one of these springs, where the accessories to the "cure" mean so much. The modified diet, freedom from business worries and cares, regular hours, proper exercise, baths, douches, etc., are important adjuncts.

Medicinal Management of the Acute Attack.—The patient should be kept in bed, where he is usually quite willing to remain owing to the severity of the pain. A mild saline laxative should be administered at the outset. The affected joint, where conditions permit, as in the case of that of the big toe, should be elevated, and wrapped in thick layers of raw cotton surrounded by oiled silk. In this way the joint is protected from accidental pressure, and the wool acts as a poultice, inducing local sweating, and also swelling, which tends to relieve the acuteness of the pain. The use of warm or cold applications locally must depend entirely upon the relative relief experienced by the patient in any individual case. Local anodynes may be tried when the pain is severe. A lotion of laudanum and water in various proportions may be applied. Whisky and water, applied quite warm, is a favorite remedy. Ichthyol and lanolin, 10 grains to the ounce, may be tried. Blisters, and counter-irritation by the use of the cautery, are rather to be avoided, although the latter may give some relief. Some have claimed that the length of an attack may be much shortened by beginning early to induce motion of the joint by either active or passive means. Few subjects are willing, however, to consent to such heroic measures. Baking in the dry oven may ameliorate the pain. It is worth while to try the effect of passive hyperæmia on the pain by the application of a tourniquet or Esmarch's bandage about the extremity above the joints, for periods of five minutes several times during the day, as recently

recommended by Bier and others in painful joint affections. In certain instances this has given great relief.

Colchicum is the drug most likely to give relief from the pain. This is so prompt in many instances that it is often referred to as a specific, in much the same sense with which we use the word in connection with quinine and mercury. It was first introduced, in 1763, by Storck, who recommended its use in gout and rheumatism, and also as a diuretic and drastic in dropsical conditions, although it is said to have been known to the Greek and Arabian physicians of the sixth century, as a remedy for gout, under the name of hermodactyl. The drug may be administered either as the wine or the tincture of the seeds, preferably the former, in 20 minim (cc. 1) doses every two hours for 4 doses, and then every four hours until the pain is relieved, unless untoward physiological effects manifest themselves. The relief to the pain is usually very prompt, but how it is effected is not at all well understood. It must be discontinued on alleviation of the pain because it is not known to have any direct action on the gouty process. Its active principle, colchicin, is also in use. The administration of colchicum may be abused and harm done. When given in excess, it causes vomiting, purgation, and cardiac depression. It sometimes happens that colchicum fails to give relief. In these cases the salicylic acid preparations may be tried. Although not so likely to give early relief to the pain as in rheumatism, yet the salicylates, which were first recommended in gout by Germain Sée, are held in high repute by some clinicians. They are known to increase the total output of nitrogen and materially to augment the excretion of uric acid. It is not agreed, however, that their beneficial effect is due to this action. They may be given as sodium salicylate, oil of gaultheria, or aspirin. The latter, the acetic ester of salicylic acid, has gained favor, and has the advantage over the ordinary salicylates in being less injurious to the stomach. It may be given in 10 to 20 grain (gm. 0.6 to 1.3) doses every two or four hours, until pain is relieved. Antipyrine or phenacetin may be tried for the pain, but must be used with caution. In certain cases where the pain is excruciating and does not yield to the usual remedies, a hypodermic injection of morphia should be administered. It is customary to give the patient alkalis during the acute attack. Their efficacy is doubtful. The citrate, acetate, or bicarbonate of potash, in 20 to 30 grain (gm. 1.3 to 2) doses every four hours, administered in large quantities of water, should be tried. Any benefit obtained is probably due rather to the water than to the alkali.

The diet is very important during the acute attack. It should be as purin-free as possible. A diet consisting of milk, eggs, butter, white bread, rice, sago, and cheese, is free from nucleins. For the first day or two, when the fever is high, it is well to restrict the patient to milk and barley-water. As the acute symptoms gradually subside, eggs and other members of the above list may be added, and when the fever entirely disappears small amounts of the white meats, such as chicken, etc., may be permitted.

When the acute symptoms have disappeared, gentle massage to the affected joint should be started, and active and passive motion encouraged. If the patient's means will permit, he should be sent to one of the mineral springs for a "cure," where the accessories are fully as important in the treatment as the drinking of the waters. Where this is not possible, a simple bitter tonic should be prescribed before meals. A common course

to pursue is to give the patient a prescription containing 5 to 10 minims (cc. 0.3 to 0.6) of wine of colchicum with the same number of grains of potassium iodide, or 20 grains (gm. 1.3) of potassium acetate or citrate after each meal and at bedtime, for two or three weeks. The patient should be induced to drink freely of water before meals and on retiring, to restrain his appetite within reasonable bounds, and to indulge in some daily exercise.

The Uric Acid Solvents.—Hardly a year passes without one of these much vaunted remedies being introduced to the medical profession. They almost invariably fail to justify the claims made for them. Just as in the case of the alkalis, this is due to these solvents failing to act in a complicated medium like the blood-serum as they do in a test-tube.

Of the organic bases claimed to be uric acid solvents, the first put on the market was *piperazin* (diethylenediamin). With uric acid it forms piperazin urate, which is soluble in water in the proportion of 1 to 50, while lithium urate is soluble in 1 to 368, and uric acid itself in 1 to 38,000. It was concluded that it would be an ideal remedy for keeping the uric acid of the blood in an easily soluble form, and also for causing a solution of the biurate deposits in the tissues, and of uric acid calculi in the kidneys or bladder. Experience has shown, however, that its administration is not followed by any increase in the uric acid output. This failure is probably explained by the observation that when several salts are added to uric acid in a test-tube the dissolving action of the piperazin is markedly reduced. The salts of the blood act in the same way. The other solvents closely related to piperazin constitutionally, *lycetol* and *lysidin*, which had a temporary vogue, particularly on the Continent, have failed to give the results claimed for them, for the same reason. Piperazin-water is still in use, but it is the water rather than the piperazin that gives rise to any beneficial results that follow its administration.

Urotropin (hexamethyltetramine) was introduced into the therapy of gout in 1898, by Nicolaier. He, with Tollens, His, and others, demonstrated that formaldehyde formed diformaldehyde urate with uric acid, which is soluble in water in the proportion of 1 to 300 to 1 to 400. When urotropin is administered to an individual it yields formaldehyde in the organism, which in part is excreted in the urine as diformaldehyde urate, —the greater part, however, in other combinations. The hope that urotropin would increase the uric acid excretion was not borne out by the analyses of Rosenfeld and Orgler, who found the uric acid actually diminished, and by Schreiber, who found it unchanged. The effect of the drug in gout, therefore, is very doubtful, although Nicolaier and Flexner claim to have seen benefit in a few cases. Any beneficial effect it may have in the treatment of uric acid calculi may, in part at least, be referred to the antiseptic action of the formaldehyde it produces in the system.

Urea has been used, but the results have been far from encouraging. Being a diuretic it may do some good, but there is no scientific basis for its use.

One would naturally think that the nuclein bases, or any allied compounds, would be the last remedies to be tried in gout therapy, knowing as we do, that uric acid is largely derived from them. One of the allied compounds, *thymic acid*, which is claimed to be "base-free," has been tried by Minkowski, who found in one case that the uric acid excretion was

increased and that there was apparently a diminution in the size of some of the tophi.

The general conclusion to be drawn from the experience with these various uric acid solvents is that they are practically all failures so far as any direct effect is produced. Their possible beneficial action results from the fact that the patients can be induced to drink more water in this way than without medication.

Remedies to Increase the Rapidity of Uric Acid Oxidation.—*Oxygen inhalations* have been tried, but the analyses of Honigmann and Krafft show that there is no diminution of the uric acid excretion, and no evidence to point toward its increased oxidation in the system. Thyroid tablets and spermin have been used for the same purpose, and with the same results. From what is now known concerning the action of various enzymes in transforming the various purin bases one into another, and of the action of a special oxidase in destroying uric acid, we may look forward with hope that some therapeutic means may yet be discovered to influence their action.

Local Measures.—These have already been considered in the management of the acute attack.

Operative Procedures.—It occasionally happens that surgical measures are indicated. When joint tophi become inflamed, and spontaneously open and discharge biurates, a persistent discharging sinus may result. In these cases eradication of the tophus is advisable. The bursæ sometimes become inflamed, swollen, and painful, and, in some instances, free opening of them gives great relief.

Riedel has recently operated on 2 cases with gouty arthritis limited to one of the great-toe joints. A mistaken diagnosis was made in both instances, the arthritis being thought to be due to a suppurative process. At operation, however, it was found that the arthritis was of gouty origin. The joint capsule was completely removed without interfering with the bone, and the edges of the operation incision were brought together without the use of sutures. In both instances the patients lived for years with no recurrence of arthritic attacks, death resulting from other causes. On the basis of these 2 cases, Riedel recommends the ablation of the capsular tissues in those instances in which the arthritis has been confined to a single joint. On such limited experience, it does not do to draw any definite conclusions as to the advisability of operative procedures. The removal of the affected joint cannot eradicate the metabolic disturbance causing the disease. Further, we know that patients often go for years without recurrences of the arthritic symptoms.

As to the use of *electricity* in the treatment of the disease, it may be noted that Remak and Benedikt claim to have obtained good results by the use of the constant current locally applied to the affected joint, both in the acute as well as in the chronic form. Labatut, Jourdanet, and Levison, have recently reported beneficial results by the use of electrical endosmosis, or kathaphoresis, with lithion, in the treatment of the joints and skin tophi. The galvanic current, with the electrodes moistened with a concentrated solution of lithion chloride, or carbonate, is passed through the affected joint or tophus, or is given in the form of an electric lithion bath.

General Management of the Chronic Cases.—The regulation of the diet stands first in importance. As we have seen, it is generally agreed that

reduction of the total food intake is of more importance than the special restriction of any one of the three varieties of foodstuffs. In the case of the proteids, those that are most easily digested, such as eggs, fish, and the white meats, are preferable. Those rich in nuclein, such as sweetbreads, kidneys, liver, and brain, should be avoided. If any change be made, the vegetables should be increased at the expense of the proteids. The patient should be regular in his meals.

Plenty of exercise, of the character already outlined, should be taken. Worry, and all unnecessary psychical disturbance, must be avoided. In the case of podagra, special care must be taken to secure a properly fitting shoe. The individual should be warmly clad. The digestion should be looked after, and any tendency to constipation counteracted.

The majority of patients do not require anything medicinally, excepting during the acute exacerbations. They must be persuaded to drink several glasses of water daily on an empty stomach. As it is difficult to get patients to do this, the object can be more easily secured by having them take some alkali, such as a 5 grain tablet of effervescent carbonate or citrate of lithia dissolved in a glass of water, several times daily.

Where the patient's means will permit, it is well to send him to one of the mineral springs for a few weeks' "cure" each year, where the accessories of the cure mean as much as the drinking of the water itself.

Treatment of the Complications.—In cases complicated by *diabetes* the carbohydrates should be restricted. The glycosuria is of a mild type and generally yields readily to dietetic treatment.

Where there are evidences of a serious *nephritis*, the proteids should be partially cut down. If uræmic manifestations supervene, as they often do, the usual measures for this complication should be tried.

In the cases with an increasing tendency to *obesity*, the fats and carbohydrates should be cut down, and proteids permitted in larger amounts than would be allowed in the average case.

The *cardiac complications* require especial attention. In the cases with evidences of myocardial weakness, the usual cardiac stimulants and tonics are indicated. If the condition be not a too serious one, and the patient's circumstances permit, a course of baths at the Nauheim Springs, in Germany, may help the cardiac features, and will also tend to alleviate the ordinary gouty symptoms. Where the patient cannot be sent away, a substitute may be made for the Nauheim baths by the use of the Triton Effervescent Salts, prepared in this country. Still the writer knows of patients with cardiac disease who have actually been injured by this treatment and feels that the greatest caution must be used in advising it.

CHAPTER XXXII.

OBESITY.

By JAMES M. ANDERS, M. D.

Synonyms.—Lipomatosis universalis; adiposity; corpulency; fatness.

Definition.—Obesity is a metabolic disorder, commonly assuming the form of hypernutrition, and is characterized anatomically by an excessive amount of bodily fat; it assumes clinical importance when the fat deposits throughout the body become burdensome or produce impairment of the functions, as shown by disinclination to muscular exercise, palpitation, dyspnœa, and other features. The condition is associated with, and dependent on, a variety of underlying affections; so that it may be rightly regarded as a symptom rather than a pathological entity. The far-reaching importance of due attention to this fact in the treatment of obesity is exemplified in the success which attends the removal of the causative states.

Historical.—As early as the sixth century, Cœlius Aurelenius applied, although without justification, the term *polysarcia* to this disorder. The Greeks and Romans adopted hygienic means, principally mechanical, against the development of obesity, and in their lighter literature as well as that of Persia, Japan, and China, frequent allusions are made to the "overweighted and irascible victims of gout," ardent votaries of fashion and the pleasures of the table. The subject of corpulency occupied the mind of Hippocrates, who likewise discoursed lengthily on a fatty diet. Later, Celsus made important contributions to the prophylaxis of obesity; and this disease constituted one of the principal humors of Galen's system.

The older authors entertained a just appreciation of the serious complications and sequelæ of obesity, and the burden of their instructions in the absence of therapeutic resources had to do with prophylactic measures. They noted with painful interest that important lives were shortened from the thoughtless enjoyment of vinous potations and over-indulgence in eating. The writers of antiquity, however, and this is especially true of those of the middle ages, manifested a total ignorance of the nature of the metabolic processes involved in nutritional disorders; and their methods of treatment consisted of external measures alone, such as out of door exercise, sea baths, and active hand-rubbing of the body, either respectively or unitedly.

In 1718, Rhotonet, a Parisian surgeon, "excised nine pounds of fat from the abdomen of a well-known person and thus relieved her" (Oertel). During the seventeenth and eighteenth centuries, numerous papers were published on obesity, but no real advances in knowledge either of the pathogenesis or treatment of the condition were accomplished. No definite

scientific investigations into the nature and causes of the disease were undertaken until the nineteenth century, when J. V. Liebig prosecuted valuable labors in connection with the origin of overfatness. From that time on, our knowledge of the subject of adipose tissue and nutrition was elaborated, not wholly, but principally, by the labors of M. v. Pettenkofer, Harvey, Voit, J. Munk, Vogel, Toldt, Virchow, Flemming, Leyden, Unna, von Noorden, Ebstein, and Oertel.

These authors have experimentally established the origin of fat from carbohydrates, albumin, and fats, and, moreover, have elucidated the causes and pathological processes involved in nutrition, hypernutrition (fatness), and subnutrition (leanness). Perhaps most disagreement existing between investigators in this field has reference to the histological relations of adipose tissues. A few epoch-making events stand out prominently. Thus, Leyden showed the important and far-reaching connection between coronary artery disease and certain myocardial lesions met with in fatty overgrowth. Another, and practically a first, step in advance in our therapeutic resources, was the introduction of thyroid-feeding in the treatment of this disease.

The recent literature of nutrition has attained to considerable proportions and among the most valuable researches on the subject are those of Moleschatt, Ranke, Voit, and Forster, whose combined studies have given us an accurate determination of the food requirements under normal conditions. Metabolic investigations have also proved that obesity may result from inordinate stimulations of the physiological functions due to over-alimentation as well as by all the processes which tend to slow the organic oxidations.

Varieties.—Two leading forms are recognized: the plethoric and the anæmic. These may merge into a third, or hydræmic, form, and there are many transitions between the two typical varieties. The anæmic variety reaches the hydræmic stage much earlier than the plethoric, and, according to personal experience and observation, only a fragment of the cases composing the plethoric group merge into the terminal stage of the disorder. These differences in the general course and tendencies of the different varieties of obesity will become evident on noting the causes to which they are attributed. A division of the cases of obesity into general and local should also be attempted in practice (*vide infra*).

Etiology.—Certain *predisposing causes* should be prominently mentioned,—heredity, age, sex, sedentary occupation, temperament, enforced rest, habit, and climate.

Predisposing Causes.—*Heredity.*—*Heredity* was clearly traceable in 330 (or 60.7 per cent.) of 543 cases occurring in the writer's experience, and, in some instances, through several generations; it cannot be said to depend upon the indolence of ancestors so much as upon peculiarities of the digestive and assimilative powers. In this group, a history of gout among the antecedents is also commonly observed. Thus, podagra due to heredity or in actual association with the obesity was noted in 235 (or 43.2 per cent.) of this series of 543 cases. "Rheumatism" was present in 104 (or 35.5 per cent.) of the cases. These figures indicate a close and vital connection between gout ("rheumatism"), and obesity.

Hereditary disposition to gout having been established beyond peradventure, may serve to explain why heredity is commonly noted in obesity,

In general terms, it may be said that gouty subjects, in whom a moderate degree of obesity is frequently associated, manifest a reduced oxidizing energy, as evidenced by a low hæmoglobin content of the erythrocytes. In many instances of the sort the red corpuscles are normal or even increased, while the hæmoglobin percentage may be as low as 70. *Per contra*, the assumption advanced by Oertel, that "persons whose albumin-bearing tissue, especially muscular and glandular tissue, exhibits a strong power of growth, in order to satisfy the cellular vital requirement, are, therefore, less liable to become obese than others whose hereditary constitution lacks this energy of growth and nutrition," is fully confirmed by the observations of the writer. Again, granted that a preformed fatty tissue exists as an independent organ, inherited qualitative peculiarities would account for the predisposition to an abnormal accumulation of fat in some cases at least. This view is supported by the fact that the definite parts showing normally the largest fat deposits, are primarily those in which excessive or abnormal accumulations principally occur.

Hereditary predisposition manifests itself early in life by the appearance of well-marked corpulency, but it may not show itself until a later period or until some trivial exciting cause becomes operative. An inherited taint is more commonly observed in females than males. Atavism may occur. With Kisch, Oertel, and others, the writer agrees that heredity is not more pronounced in the same sex (*e. g.*, from father to son, and mother to daughter,) since his collective investigations tend to disprove this claim.

Age.—The general tendency to an abnormal accumulation of fat is more pronounced at certain periods of life than others; but this variability may not be dependent on the age *per se*, inasmuch as it is difficult to disassociate the influence of habit, alimentation, and many other factors. In young infants, a marked degree of obesity may occur, and in many cases it is principally ascribable to the milk and farinaceous articles of food consumed in the diet. This form of infantile corpulency is apt to disappear subsequently, although it may reappear later on in life, especially when a radical change in the habits occurs.

On the other hand, in a certain proportion of the cases of obesity commencing at birth, a slow and gradual increase in the amount of fatty tissue may take place during childhood and adolescence. In the majority of instances, however, corpulency develops later in life, in the male during the period between forty and fifty years, and in the female during the two decades between thirty and fifty years. The favoring influence of puberty apart, during adolescence, a period of life in which enormous quantities of nutritive material are demanded by the organism, the tendency is toward a decrease of adipose tissue. Again, in advanced years, when retrograde metabolic processes occur, the conditions favoring an abnormal accumulation of fat are missing.

Sex.—Obesity, under normal conditions of life, is more common by far in the female than in the male. Personal experience and observations confirm the view that, owing to the lower percentage of hæmoglobin in women in comparison with men, the oxidizing energy is correspondingly diminished, and hence a greater tendency to transformation of the carbohydrates into fat is the natural consequence. In the causation of obesity, a prominent role is ascribable to childbirth. The condition dated from the puerperium in 16.2 per cent. of the writer's series in females, and

from miscarriage in 5.3 per cent. In multipara, each subsequent pregnancy increased the general tendency to obesity, in some cases at least.

Other factors expressly favorable to the development of an abnormal amount of fat in the female are: The more quiet, inactive life, the greater tendency to indulgence in fat-forming articles of diet, puberty, and the menopause (slight). With reference to the menopause, Tilt's statistics are significant: He studied 382 cases in women in whom the menstruation had completely ceased for five years, and found that 121 had grown heavier, 171 had retained their former weight, while 90 had become lighter. When the menopause leads to greater corpulence it is manifested especially by the acquisition of an *embonpoint*. While the anæmic type of the disease is more common in the chlorotic female, more cases of the plethoric type are met with in the male.

Temperament, Occupation and Enforced Rest.—The indolent, sluggish, luxury- and rest-loving, phlegmatic individual is disposed to corpulency. This fact affords a satisfactory explanation why obesity is so commonly observed among certain races—southern Italians, Orientals, South Pacific Islanders, Dutchmen, and certain African races. Similarly the inhabitants of low countries of the temperate and arctic regions, living, as they do, under conditions favorable for the development of the phlegmatic temperament, are prone to abnormal fat-deposition. In phlegmatic persons there is an additional factor of importance; they are quite generally inclined to consume large quantities of fat-forming substances.

The occupation may exert no inconsiderable effect, a sedentary life favoring the development of corpulency. Any calling in which the required muscular activity is at a minimum predisposes to adiposity. The condition often dates from longer or shorter periods of enforced rest—*e.g.*, following accidents and illness; the hemiplegic is often obese owing to muscular inactivity. Following such acute infectious diseases as typhoid fever, pneumonia, acute articular rheumatism, and the like, adiposity, especially of the anæmic form, not uncommonly develops. The writer's notes indicate that this is a rather potent factor; thus, out of a total of 543 cases, 43 (or 7.9 per cent.) followed an acute illness. Among incidental predisposing causes should be mentioned congenital anomalies and monstrosities (idiots, cretins, acephali).

Exciting Causes of Obesity.—Obesity is especially dependent on the habitual ingestion of abnormally large amounts of fat-making food, and the intemperate use of alcoholic beverages—sweet wines, beer, ale, and porter, in particular,—with or without deficient exercise. The source of the fat is considered to be the fats and carbohydrates taken as food, although probably it is derived to a considerable extent also from the albuminoids. "One product of the decomposition of albuminoid substances is invariably fat" (Strümpell). A striking illustration of an increase of adipose tissue from proteids is seen in the present-day method of treating cases of tuberculosis with milk and raw eggs. An excessive diet of starches and sugars acts indirectly as a fat-producer by lessening the oxidation of the fats and proteids which may be ingested, because the carbohydrates themselves are so readily oxidized. Hence excessive indulgence in any one of the several varieties of diet may produce the condition.

Intemperance in the use of alcohol plays an important role by inducing hypernutrition. In such subjects, however, there may be observed an impaired appetite for the articles of food that enter into the everyday dietary, and poor digestion. Alcohol is readily oxidized in the system, thus allowing the fat previously present to remain undisturbed. Alcohol also prevents tissue-waste; and finally, certain beverages, as beer, contain starches in considerable amount. It has been estimated that a person taking habitually 5 or 6 glasses of beer daily, would consume $5\frac{1}{2}$ ozs. (150 gm.) of starch, or about one-half of the required amount, in the same period.

The intemperate, on account of physical torpor which is the necessary result of his habits, is notably disinclined to pursue muscular exercise. Neither has he sufficient endurance to adopt the proper forms of exercise to maintain healthy nutrition. Familiar illustrations of the effects of intemperance in this regard are afforded by inn-keepers, brewers, and the inhabitants of certain countries, like Germany and Bavaria, in which beer-drinking is in vogue.

In this connection emphasis should be placed upon the occurrence of localized depositions of fat as a pathological process, probably dependent on the same laws which produce general obesity.

Special Pathology.—The most obvious change is the decided increase in the adipose tissue throughout the body. The fat deposits are most marked in localities in which fatty tissue is normally present, as under the skin, in the panniculus adiposus, and the mammary regions; they also occur in the various internal organs and tissues that are altogether, or almost, free from fat in healthy individuals.

The physiological amount of fat has been estimated by Beclard and Quesnay at no more than 5 to 6 per cent. of the whole weight in adults, while the proportion of fat in the new-born varies between 9 and 18 per cent. The normal fluctuations are greater in women (to whom the higher figures also pertain) than in men, and a moderate increase of fat beyond the percentages given above, after the fiftieth year, may be regarded as a physiological condition. The variations in the amount of fat that occurs within the limits of health are dependent on age, climate, and family and racial characteristics.

The deposition of fat which always occurs in the connective tissue greatly increases the bulk or dimensions of the body. The round face, "double chin," bulky, deep chest, large waist, conspicuous and sometimes pendulous abdomen, and short, thick, cylindrical limbs, are familiar appearances. Again, the trunk is often disproportionate to the extremities. Children may be obese, and the disorder is rarely congenital. It is to be observed that corpulency, "fatty infiltration," and "fatty degeneration," are not synonymous terms.

The various viscera, more particularly the *heart*, are overlaid with fat, and the interstitial connective tissue may be the seat of fatty infiltration. In subpericardial overfatness, as seen in extreme general obesity, particularly of the anæmic variety, fatty infiltration of the intermuscular tissue of the heart may supervene. Out of 103 cases, lasting for periods ranging from a few to many years, of extreme adiposity that have occurred in the writer's experience, only 5 cases gave clinical proof of the

existence of true fatty infiltration.¹ On the other hand, in cases of excessive obesity this morbid process (infiltration) is limited to a thin layer of the intermuscular fibrous tissue, situated directly beneath the epicardium; but it is not to be confounded with true fatty infiltration.

In exceptional instances fatty infiltration may terminate in fatty degenerative change of the muscle cells. In extreme grades muscular atrophy from compression by infiltrated fat ("pressure atrophy") may also ensue. In this article, however, we are concerned only with the alterations that belong to "fatty overgrowth." Hypertrophic dilatation of the heart is frequently present in high degrees of plethoric adiposity, owing to an enlarged volume of blood, and the arteries may show fatty changes in the intima and media, and later those of arteriosclerosis. The arterial changes may lead to the development of chronic interstitial nephritis, which thus becomes a late complication of obesity. The *veins* are often the seat of larger or smaller varicosities. The *kidneys* and *lungs* may be enlarged owing to fat deposits and fatty infiltration. Additionally, passive congestion and œdema of the lungs, secondary to the cardiac weakness, may be found at autopsy. Of the viscera, the *liver* alone is the seat of normal fat deposits, but in obesity these accumulations may cause enlargement of the organ. The *stomach* may be dilated, and a catarrhal gastritis and enteritis is sometimes observed.

The *blood changes* vary with the different forms of corpulency, hence they will be considered separately: (1) In the plethoric variety the mass of blood is abnormally large. The whole blood shows an increase in specific gravity, fluctuating, however, between 1.062 and 1.070, and that of the serum between 1.032 and 1.035. There are cases in which the number of red cells reaches an extraordinary degree. In one of the writer's patients the red cells numbered 6,800,000 per cmm.

Pathogenesis.—Fats conserve the albumin in metabolism by furnishing heat and force during their combustion—an important chemico-physiological function. By thus favorably affecting the metabolic processes, they at once rise to an important position in connection with the general nutrition, and a certain proportion of systemic fat is naturally essential for the preservation of health. (See also PATHOLOGY, *supra*.) The origin or mode of formation of the excessive fat accumulations is a subject that is imperfectly understood. In the plethoric form of the complaint, obesity most probably results from the ingestion of an excessive amount of fat-producing carbohydrates and their complete transformation owing to an abnormally active digestion and assimilation. *Per contra*, in the anæmic variety a deficiency in the oxidizing power of the system may be assumed to exist and constitute the principal factor in bringing about the condition. Under these circumstances, a normal proportion of carbohydrates in the aliment used will fail to be destroyed on account of deficient oxidation. Obesity, therefore, may be said to be dependent on disturbance of cell-activity; and the overuse of carbohydrates leads oftentimes directly to an excessive manufacture of fats. The liberal consumption of proteids may also result in a fat-forming residue, which, if not destroyed by oxidation, may produce adiposity. The disturbance of the metabolic processes that leads to deposition of fat, may be transmitted through heredity.

¹ *The American Journal of the Medical Sciences*, April, 1901.

According to Toldt, "fatty tissue" is regarded as a special organ; this "preformed adipose tissue" may undergo an increase as the result of a proliferative process. Again, connective tissue cells, which penetrate between the elements of organs, may be transformed to "fatty tissue," forming the condition known as fatty infiltration; but this does not usually fall within the scope of physiological conditions. Oertel¹ correctly states that the fat arising from this process is most damaging to the physiological functions of the vital organs.

Histology.—Microscopically, differences in the size and number of the fat-globules are exhibited. Thus, in the plethoric form of polysarcia the fat-globules are large, being distended with droplets of fat; their cell envelope and nuclei, however, are quite indistinct. When numerous, the fat-vesicles are closely packed and their surfaces are faceted by mutual pressure. They are round, or ovoid, or (less commonly) oblong when sparsely scattered through the connective tissue. On the other hand, in cases of the anæmic or hydræmic variety of corpulency in which the fat-masses are soft and doughy to the feel, the cells are less completely filled with larger or smaller droplets, and the cell membrane and nucleus are easily distinguishable.

The process of fatty infiltration begins with the appearance of a small droplet within the cell envelope; this grows larger until "the cytoplasm forms a mere capsule about it and the nucleus is crowded and flattened in consequence." Microscopic sections, stained in the usual manner, do not show the presence of fat-globules, but in the spaces previously occupied by them vacuoles are seen.

Symptoms.—Owing to the insidiously progressive character of the affection, and the absence of all characteristic prodromes, it is exceedingly difficult to fix the date of the onset as a clinical entity. At first, slight inconvenience, a sense of burdensomeness, and dyspnœa during walking or working, are the principal subjective manifestations, and, indeed, no other symptoms may be complained of for years. Later, with the slow and gradual development of the disease, and involvement of the various viscera, both the number and intensity of the clinical features are increased. Marked breathlessness on exertion, due to the hampering of the action of the heart and lungs by massive chest-walls, fat-overgrowth and the upward-crowded diaphragm, are among the earliest conspicuous features. The symptoms presented by individual patients will vary according to the stage at which they come under observation. Again, the two leading varieties—plethoric and anæmic—of obesity present diametrically opposed conditions of the blood as a basis for the abnormal fat accumulations, and hence both the external appearances and the subjective manifestations are quite dissimilar. For these reasons the two typical forms demand separate consideration.

1. Plethoric Form.—In this variety there is hypernutrition of all the tissues. Such patients often partake of large quantities of beer or other fluid during meals and the appetite is abnormally keen. In addition to the excess of fat, which is symmetrically distributed throughout the body as a rule, the muscles, including those of the myocardium, are vigorous and voluminous. The blood shows a condition of abnormal richness both in

¹"Obesity," *Twentieth Century Practice of Medicine*, vol. ii, p. 658.

erythrocytes and hæmoglobin. In a number of patients the erythrocytes are over 6,000,000 and the hæmoglobin over 110 per cent.

Physical Signs.—The general appearance indicates robust health and unusual vigor of constitution. The complexion is florid, the skin soft, smooth and in some cases the face looks congested; the lips, conjunctivæ, and other mucous membranes present a rosy hue. The neck is massive, the abdomen prominent, and the girth decidedly increased. The sweat-glands are unusually active. But though the systole is abnormally strong, the impulse is felt indistinctly on account of fatty-overgrowth and the subcutaneous depositions of fat. Later, as the result of myocardial weakness, and often before this in extreme cases, the impulse may be lost, both to inspection and palpation. The pulse is slow and of high tension; this causes arteriosclerosis with its usual consequences—cerebral hyperemia, cardiac asthma, chronic interstitial nephritis, anginal seizures, and finally apoplexy. The vigorous contractions of the heart, due to muscular overgrowth, sooner or later grow feeble as the result of cardiac failure, the pulse declines in fulness and volume and finally becomes small and arrhythmic. Bradycardia is a not infrequent concomitant (*vide infra*).

Indications of cardiac enlargement are present. In well-marked corpulency, however, it is always difficult, and sometimes impossible, to establish the boundary lines of dulness by percussion. The heart sounds remain clear for a long period, but with the progressive development of the condition become indistinct. Murmurs may be audible, most commonly in the aortic zone; they are probably not due to chronic valvulitis, but to either a roughened condition of the intima of the aorta or to relative incompetency, other indications of a dilated heart being then in association. Again, the bruit may rarely be hæmic in origin or “due to an abnormal, relaxed state of the heart muscle, or to weakness or insufficiency of the papillary muscles.”¹

In advanced cases, arteriosclerosis, affecting particularly the aortic arch and the coronaries, is an associated lesion of comparative frequency. Forchheimer noted it in 39 out of 122 cases of fatty overgrowth found in the literature prior to 1889. Of these, atheroma of the aorta occurred in 21, and similar lesions of the coronaries in 14 cases. When atheroma occurs, accentuation of the second aortic sound is noted, and in cases showing involvement of the coronaries arrhythmia is conspicuous.

In many cases the condition does not proceed beyond a moderate grade of obesity, and the patient enjoys good general health. He, however, does not resist well the inroads of the acute infections, and his fat-laden viscera are likely to show degenerative changes at a premature period of life.

In another contingent of cases belonging to this variety, the condition, if unchecked, leads to a marked increase of the general bulk of the body and various grotesque malformations. The features are broad and coarse, and some of the facial lineaments are obliterated. Indeed, the natural folds of the skin everywhere may be substituted by those formed of huge layers of fat. The fat-deposits are most prominent about the neck, and the double and triple chin are readily noted; also over the trunk and particularly the abdomen, which may be markedly pendulous. The

¹ See Schroetten, *Ziemssen's Hand-book*, vol. i, p. 26.

maximum weight among the writer's patients was 412 pounds, and Weinberger observed a boy aged ten years weighing 266 pounds. The bodily movements become slow and clumsy, and the gait wabbling, heavy, and somewhat uncertain. At last locomotion may be impossible, partly from the increasing weight of the fat and partly from the extreme feebleness of the tissues, particularly those of the heart.

In some cases the muscular power diminishes rapidly, the appetite fails, profuse sweatings occur, and signs of general venous stasis may be observed. In the majority, however, venous engorgement develops more insidiously. Cough, distress of respiration, and asthmatic seizures, especially at night, signal the passive hyperæmia of the respiratory mucous membrane. The symptoms of a gastric catarrh, dependent on stasis in the mucous membrane of the stomach, are in evidence, and with these the characteristic features of gastrectasis may be combined. Great thirst and bulimia may be observed in some cases at least. From analogous changes in the intestines, there is often constipation which may alternate occasionally with diarrhoea. The passive congestion of the kidneys is shown by a tendency to oliguria with albuminuria, and the presence of hyaline and a few granular casts.

As elsewhere stated, the poisonous products of tissue-metabolism are not eliminated in the normal ratio. Indeed, in one female patient, aged forty-two years, presenting marked obesity, weighing 225 pounds, although otherwise feeling in good health, the daily renal output was diminished one-half from the health standard. The amount of food ingested was plus. Sexual desire is in abeyance and azoöspemia is not uncommon.

In the last stage of the plethoric kind of obesity, malleolar œdema merging into progressive dropsy may arise. As the result of judicious treatment the arterial pressure may steadily rise and at the same time all of the clinical phenomena dependent on the venous stasis gradually disappear. In the end, however, owing to fatty changes taking place in the myocardium, permanent results are out of the question, and a fatal termination is reached amid the signs and symptoms of advanced cardiac dilatation. Death may also come suddenly from cardiac paralysis.

2. Anæmia Form.—This leading type is characterized by and dependent on anæmia, often of chlorotic type. Cases of the plethoric form merge into this variety; it may, however, require many years for this. It is to be noted that while extreme degrees of the anæmic form of overfatness may be encountered, the fatty depositions do not reach the gigantic proportions of the opposite variety. Muscular exercise is difficult and early induces exhaustion, accompanied by distress of breathing and cardiac palpitation.

The symptoms are in a measure those characterizing the anæmias in general, together with a peculiarly marked increase of fatty depositions in the usual places of predilection. The writer has the records of a blood examination in nineteen cases. In the majority of the instances the blood changes were of the chlorotic type. The hæmoglobin percentage varied greatly—from 33 to 83 per cent.—the average being about 70 per cent. In about 35 per cent. of the cases, however, the erythrocytes and hæmoglobin were reduced about equally. More or less poikilocytosis was commonly found; and also an occasional normoblast and a considerable leukocytosis (the count ranging from 11,000 to 31,000 per cmm.) was present in about 25 per cent. of the cases.

The *physical signs* are at variance with those found in the plethoric form. Inspection shows pallor of the bodily surface and the visible mucous membrane. The skin is inclined to free perspiration, and, in advanced cases may become wrinkled. "The skin is often irritated (intertrigo) by the excessive sweating, and by the friction of cutaneous surfaces in the folds of fat, as under the breast, at the abdominal and inguinal folds, and around the scrotum and labia. This may be followed by eczema. Painful excoriations, pruritus, acne rosacea (in alcoholics), and alopecia, are also not uncommon." To the feel, the subcutaneous fat-cushions are soft and flabby, and the muscles are lacking in firmness and strength. Irregular, circumscribed fat-masses, in the subcutaneous tissue, ranging in size from a split bean to a hen's egg, are sometimes palpable. Apart from the augmented peripheral blood-tension, which is common to the anæmias, the signs of cardiac insufficiency become more or less conspicuous with the progressive development of the condition, and at last, as the result of falling arterial pressure, dropsy supervenes. In two instances under personal observation marked anasarca finally developed. The characteristic hæmic murmurs, as well as the *bruit de diable* in the cervical veins, are often heard.

While it is generally conceded that the principal factor in the production of this form of obesity is the anæmic condition of the blood, or, in other words, that it is dependent on the feeble oxidation resulting from the greatly reduced hæmoglobin-content of the erythrocytes, it is to be recollected that greatly impaired nutrition with associated anæmia and defective combustion of fat may likewise arise from habitual muscular inactivity coupled to the employment of insufficient nourishment. As stated under Etiology, most cases of anæmic obesity occur in females, and it often originates in an attack of chlorosis during the "teens." It is probable that recovery in many chlorotic females is incomplete, and thus the foundation is laid for the future development of the anæmic type of corpulency. This is especially true of cases of chlorosis characterized by anomalies (hypoplasia) of the blood-vessels and genitalia. In such instances the menses may be both scanty and irregular, and dysmenorrhœa may form the burden of complaint.

The appetite is impaired and capricious; in most cases carbohydrates are preferred to proteids. The tongue is furred and the breath often foul. Intestinal flatulence with more or less constipation is the general rule. The daily quantity of urine voided is small, due to diminished arterial pressure. Slight albuminuria is often found and is to be ascribed to passive hyperæmia of the renal vessels in the majority of instances, since, with improved tonus of the circulation as the result of the use of cardiac stimulants, the albumin usually disappears. Attacks of intercurrent diseases are badly borne.

Complications and Sequelæ.—These have for the most part been stated, but their enumeration here will serve to emphasize the marked effect which they sometimes produce on the general course of the affection. Among the principal complications, often the precursors of the terminal stage, are bronchitis, pulmonary congestion, aginal attacks, cardiac asthma, hernia, albuminuria, glycosuria, arteriosclerosis, œdema, cerebral hemorrhage, and Cheyne-Stokes respiration. It should be stated that the cardiac asthma, which is sometimes a troublesome concomitant, is dependent on pulmonary congestion as the result of "light" breathing and feeble heart action during sleep.

The writer has seen the vascular tension apparently increased, due to stimulation of the vasoconstrictors despite a progressive loss of contractile energy of the left ventricle. Severe attacks of angina are also observed. Thompson says, "Such attacks may appear as a result of sudden dilatation, or be apparently unprovoked." The arterial pressure, however, slowly and gradually falls, as before stated, with the progress of the disease, as shown by the diminished secretion of urine and the sphygmographic tracings.

From the writer's studies, true fatty infiltration may occur as a sequel of fatty overgrowth, but it is extremely rare (*vide supra*).

Circumscribed Obesity.—In many cases the fat-depositions are not distributed regularly over the entire body, but are confined to circumscribed portions—for example, the abdominal parietes, the mammary regions, and the hips. In other patients the fat-content is in excess in the trunk, while other parts of the body—the extremities—are about normal. Williams¹ points out that localized superfluous fat-deposits are due to lack of exercise of the underlying muscles, and attributes the "abdomenia figure" to insufficient exercise of the muscles of the abdomen. The precise causes for the localization of the depositions of fat in certain portions of the body are difficult to determine. The increased thickness of the fatty layer in the abdominal wall may be due to multiple pregnancies. Again, in cases of obesity in which the reduction process is too rapidly carried on, marked inequalities in the distribution of the fatty layer may be observed.

Diagnosis.—This is not difficult in the majority of instances, but it should include the particular variety of obesity present—for example, whether anæmic or plethoric. Care must also be exercised in detecting associated conditions, as gout, anasarca, arteriosclerosis, and the like; also the complications and sequelæ. Myxœdema should not be mistaken for polysarcia, but this mistake has occurred. In both affections the general bulk of the body is greatly increased, but in myxœdema the skin is thick, firm, and inelastic; it is dry and rough and the facial lines of expression are obliterated. Again, in the latter disease the physiognomy is altered to a remarkable extent, while the lips, tongue, nostrils, and mouth, are all thickened by infiltration. Moreover, in myxœdema the voice is monotonous, slow, and has a leathery tone.

Prognosis.—The prognosis will depend principally upon the degree, variety, and prevailing complications of each individual case. In the earlier stages of the plethoric type, particularly in cases in which there is not a history of strong hereditary predisposition, but the ingestion of too much fat-making food is the principal cause, the outlook is positively favorable under appropriate treatment. In more advanced cases, with associated arteriosclerosis, particularly of the coronaries, stenocardia, and œdema, the prognosis may be of the utmost gravity.

On the whole, it is less favorable in the anæmic or hydræmic form than in the plethoric. Many of the former variety, however, are curable in proportion to the removability of the cause—the anæmia. The tendency to relapse in all cases, even those in which an apparent cure has been effected, must be recollected. In general, the results of treatment will

¹"Some Aspects of Obesity," *The Practitioner*, May, 1904.

depend upon the degree of care and coöperation which the patient is willing to exercise. Conversely, the effect of treatment upon the strength and nutritive equilibrium of the patient bears upon the prognosis. Medical officers of life assurance companies recognize obesity as an indication of impaired health, and when the body-weight is decidedly disproportionate to the height of the individual, the risk is usually declined. Such subjects bear serious illnesses of all forms, accidents, and surgical operations, badly.

Oertel's experimental test, the comparison of the fluids regularly taken and of the quantity of urine regularly secreted within the twenty-four hours, supplied a most reliable indication in cases of anæmic obesity with heart-inefficiency, hydræmia, or œdema. The patient takes as much fluid as he is accustomed to, during two days, and the amount of urine secreted is carefully measured. During the next two days the fluids taken are reduced to a volume of from 700 to 1,000 cc., according to the patient's size, and the urine again estimated. If now the quantity of urine secreted shows an increase over that of the previous two days, we may draw the inference that both the heart-power and the function of the kidneys are in a responsive condition, and therefore the prognosis is comparatively better than if the reverse as to the quantity of urine secreted should obtain.

In the writer's experience, the effect of physical exercise upon the circulation and respiration has formed a reliable criterion in the individual case. When physical exertion induces early breathlessness, thoracic oppression, and palpitation, and the pulse becomes small ("thready") and irregular, the outlook is gloomy.

Modes of Death.—Among the commoner causes of death are: Angina pectoris (from involvement of the coronaries), apoplexy, syncope, uræmia, cardiac dilatation, intercurrent acute infections, and necessary major operations. Of the rarer modes of death may be mentioned rupture of the heart, cerebral thrombosis, hemorrhagic infarctions, cardiac asthma, carbuncles (to which subjects of obesity are liable), and pulmonary congestion or œdema.

Treatment.—Prophylaxis.—A child of a mother suffering from anæmic obesity should be nourished by a suitable wet-nurse who is not predisposed by heredity to this form of polysarcia. In the earlier years of persons showing a hereditary disposition to corpulence, the fat-forming (farinaceous) substances must be greatly restricted in the dietary. The proportions of fat and proteid allowed will depend upon the amount of muscular activity. Physical exercise should be advised and encouraged, but it is to be carefully regulated. Cool bathing is a useful prophylactic measure if carried on systematically and regularly. If anæmia be associated with a pronounced tendency to obesity during childhood or adolescence, suitable forms of iron should additionally be administered.

At middle life, in those disposed to corpulency, all imprudences in eating and drinking should be cautioned against, and the quantities of various articles of food and the time of eating regulated. Outdoor sports and gymnastics should also be gauged accordingly. Prophylactic measures, however, must have reference to the special indications presented by individual cases. For example, the inclination to corpulency may be overcome by instituting measures preventive of the development of gout.

Attention to the condition of the blood and blood-making organs has also proved effective. As a rule, however, the dietetic-mechanical treatment under strict surveillance must be combined.

The *treatment of confirmed obesity* may be conveniently discussed under three heads: (a) the dietetic treatment; (b) the mechanical management (to increase oxidation); (c) the medicinal measures. There are few diseases that the physician is called upon to treat in which it is so vitally important to adapt the treatment to special cases as in obesity, and, as Grocco wisely states, it must be varied from day to day to respond to indications as they arise. If the dominating etiological influence is removable, this should be accomplished in the first instance and then attention given to the minor factors. Cases that present complications of various kinds may prohibit the exercise of the rule mentioned above. The foregoing remarks apply particularly to moderate grades of the plethoric variety of obesity. On the other hand, in well-marked cases in plethoric patients and in the anæmic type, a more complex group of indications is presented, and usually two of the elements of treatment indicated above, (a) and (b), are prime requisites. Finally, that method must be selected which invigorates while at the same time it involves neither injury nor weakening of the patient.

Dietetic Treatment.—The dietetic treatment is all-important. The diet chosen must maintain the equilibrium of the metabolic processes. Broadly speaking, the principal variation from the ordinary dietary consists in a restriction of the fat-forming food, or carbohydrates. The carbohydrates should not be totally withdrawn, since the ingestion of large amounts of proteid foods, which are difficult of complete metamorphosis, may excite digestive disturbances, gouty manifestations, and even chronic interstitial nephritis. It is the writer's almost invariable custom to allow a limited proportion both of carbohydrates and fat, and thus accomplish two objects: (1) a slow consumption of the previous fat-depositions; (2) maintenance of the normal metabolic processes.

The principal systems of dietary are known by the names of Banting, Ebstein, and Oertel. In so-called "Bantingism," sugars, fats, and starches, are greatly restricted in the dietary; water, however, is not reduced, and wines and spirituous liquors are allowed. Sir Dyce Duckworth¹ has well said that as a system "Bantingism" is both unphysiological and impractical. In subjects of a rheumatic or gouty diathesis Banting's heavy proteid and alcohol dietary, since it fails to secure complete elimination of waste products, which are now in excess of the normal, is wholly contra-indicated. A brief reference may be made to the Salisbury treatment, which in many respects is similar to the Banting, and consists in permitting large quantities of animal food (withholding carbohydrates altogether) and large amounts of *free* hot water to wash out the increased nitrogenous metabolic products from the system.

In Ebstein's diet-list the proteids are diminished, and carbohydrates greatly restricted, while fat is freely permitted. It is assumed that fat does not increase stored fat, while at the same time it tends to impair the appetite; and, being less readily oxidized than the carbohydrates, it interferes less with the metabolism of the proteids. Saccharine matter and

¹"Obesity," *Allbutt's System of Medicine*, vol. v, p. 617.

potatoes are strictly forbidden. The following is an illustration of Ebstein's dietary:

Breakfast, 6 A. M. in summer, 7:30 A. M. in winter.—White bread, well toasted (rather less than 2 ounces), and well covered with butter. Tea, without milk or sugar, 8 or 9 ounces.

Dinner, 2 P. M.—Soup made with beef-marrow. Fat meat, with fat sauce, 4 to 5 ounces. A moderate quantity of asparagus, spinach, cabbage, peas, or beans. Two or three glasses of light white wine. After the meal, a large cup of tea without milk or sugar.

Supper, 7:30 P. M.—An egg, a little roast meat, with fat. About an ounce of bread, well covered with butter. A large cup of tea, without milk or sugar.

The Oertel method of feeding, more particularly with modifications to which attention will be called hereafter, is especially adapted for some cases of obesity with feeble hearts. This author allows more fat than Banting, but less fat and more (about double the quantity) proteids and carbohydrates than Ebstein. The amount of *free* water permitted daily is only one pint; about one pint additional in other food is allowable. His diet-table for obesity is appended:

	Albumin	Fat	Carbohydrates	Calories
Minimum	156	25	75	1180
Maximum	170	45	120	1608

Oertel also offers a special diet list in circulatory disturbances, combined with graduated exercise and a marked reduction of the amount of liquid taken; it comprises three parts:

1. The reduction of the amount of liquid taken with meals and during the intervals, the total for each day being 36 ounces (1,064 cc.). Frequent bathing (including the Turkish bath in suitable instances) and pilocarpine are employed to promote free diaphoresis.

2. The diet is composed largely of proteids, as follows:

Morning.—A cup of coffee or tea, with a little milk—about 6 ounces (178 cc.) altogether; bread, 3 ounces (93 cc.).

Noon.—Three to 4 ounces (90 cc. to 120 cc.) of soup; 7 to 8 ounces (218 cc. to 248 cc.) of roast beef, veal, game, or poultry; salad or a light vegetable; a little fish; 1 ounce (32 cc.) of bread or farinaceous pudding; 3 to 6 ounces (93 cc. to 186 cc.) of fruit for dessert. No liquids at this meal, as a rule; but in hot weather 6 ounces (178 cc.) of light wine may be taken.

Afternoon.—Six ounces (178 cc.) of coffee or tea, with as much water. An ounce of bread as an indulgence.

Evening.—One or two soft-boiled eggs, 1 ounce (32 cc.) of bread, perhaps a small slice of cheese, a little salad, and fruit; 6 to 8 ounces (178 cc. to 236 cc.) of wine, with 4 or 5 ounces (120 cc. to 148 cc.) of water (Yeo).

3. Graduated exercises, as walking, the distance to be undertaken each day to be carefully specified and frequently, though gradually, increased. A like plan is to be pursued with reference to the degree of inclination. This is the most important part of the system, since it invigorates the heart muscle.

The "mechanical" part of the Oertel method also tends to consume the superfluous fat of the patient's body, and stimulate the elimination of fluid through the skin and kidneys, at the same time oxidizing the food ingested so that further deposition of fat is prohibited. It has gained an enviable reputation in Europe (*e. g.*, Germany, Austria, and Switzer-

land,) where special sanatoria for its administration have been established. At these "Terrain curorte" are to be found, "health paths" of four different grades, differing in slopes from 5° to 20°. The majority of these paths are provided with colored sign-boards giving distances and elevations, so that the exercise prescribed by the physician can be systematically and accurately followed.

A. W. Perry¹ has well said that there are cases in which an excessive amount of water (serum) in the tissues is practically the sole cause of the corpulency. He recommends Ranke's normal diet; namely, meat, 280 gm.; fat, 100 gm.; bread, 400 gm.; and the limitation of the amount of fluid ingested, allowing only 300 or 400 cc. more of water to be taken daily in drink and food than the daily amount of urine secreted. In order to carry out this method the percentages of water in different forms of food prepared ready to be eaten must be carefully estimated. These are, "(Numbers indicate percentages of water): Soup, 91.6; boiled meat, 70; roast mutton, 74; roast beef, 59; roast veal, 78; dried meat, 40; fish, white, 74; pudding, 48; mushes, 80; bread, hard, 30; bread, soft, 40; carrots, boiled, 82; spinach, 83; peas, 69.5; lettuce, 97; fresh fruits, 85; string beans, 88; celery, 84; asparagus, 94; milk, 87; cream, 65; cheese, 35; baker's toast, 1.18; crackers, 7.50; potatoes, boiled, 70; turnips, boiled, 82.5; cabbage, 85."

Labbe and Furet² recommend a regimen from which salt is entirely eliminated, in connection with the ingestion of fluids in abundance. The organism, in order to maintain its molecular composition, rejects the excess fluid, which carries off excrementitious products.

Among other systems, those of Weir Mitchell, Sir Dyce Duckworth, Strümpell, Yeo, Dujardin-Beaumetz, and von Noorden, may be mentioned. These may serve as useful guides in some cases, but a detailed statement is not possible. Finally, it must be recollected that there is no single dietary for obesity but for the individual patient.

In all patients presenting themselves for treatment, the physician should pay special attention to the condition of the urine, blood, heart, and arteries, as well as to the previous family and personal history. Under any system of dietetic treatment the patient should be weighed accurately at brief intervals. The food should also be weighed and measured at first, but the patient soon learns to estimate by bulk the requisite quantity of each article permitted. Attention to details is essential to success, and the effect of treatment upon the general health must be noted. Fat-reduction must always be slowly progressive. If the case is one of plethoric obesity, a judicious rearrangement of the food, *e. g.*, a moderate increase of the proteid substances and a corresponding diminution of the carbohydrates, is indicated. Muscular exercise, so far as possible in the open air, must also be enjoined—walking, horseback riding, bicycling, rowing, swimming. These measures usually accomplish a successful reduction even in well-established examples of the condition. The majority belong to this type, and the writer is in the habit of ordering the following dietary, with modifications to suit the peculiarities of individual cases:

¹ *California State Journal of Medicine*, November, 1903, p. 358.

² *Revue de Médecine*, 1905. No. 9, p. 674.

Morning Meal.—Fruit—as an orange, or 2 peaches, or one-half a grapefruit (without sugar), or a sour apple, fine wheat-bread, $1\frac{1}{4}$ ounces (gm. 40); a soft-boiled egg; milk, 1 ounce (28 cc.); saccharine, $\frac{1}{2}$ grain (gm. 0.03); coffee, $4\frac{1}{4}$ ounces (120 cc.).

Noon Meal or Luncheon.—Caviare, 2 drams (gm. 8); lamb chops, sweetbread, boiled ham (cold), or fowl or game in season, 3 to 4 ounces (gm. 90 to 120); salad, 1 ounce (gm. 30) (with a small amount of French dressing); cheese, 1 dram (gm. 4); bread, rye or bran, $\frac{1}{2}$ ounce (gm. 15); fruit (except strawberries and bananas), or (instead of the latter), water, 4 ounces (125 cc.).

Evening Meal or Dinner.—Soup (clear), 3 ounces (85 cc.); fish, 2 ounce (gm. 60); roast or broiled beef, lamb, veal, or game or poultry, 4 to 5 ounces (gm. 125 to 150); one or two of the following green vegetables: spinach, string beans, green peas, celery (stewed), asparagus, raw sliced tomatoes, Brussels sprouts, $1\frac{1}{2}$ ounces (gm. 42). For *Dessert*, may take plain rice pudding, junket, cup custards (all sweetened with saccharine), or fruit (except strawberries and bananas) either raw or cooked, 4 to 5 ounces (gm. 125 to 150.). May take 4 to 5 ounces (125 to 140 cc.) of water when fruit is not used.

No fluid is to be taken at meals except as indicated above, but a glass of water on rising, and three hours after food, is permitted. During the warm season, particularly if the sweat-glands are active, an additional glass of water may be occasionally allowed. It is unwise to restrict fluids too greatly in any cases in which the proteids are given in abnormally large amounts, since it allows of an accumulation in the system of the products of nitrogenous metabolism. That more than the quantity of fluid above specified is also demanded in cases of obesity associated with a gouty tendency is not a baseless assumption.

In cases of anæmic obesity, the restriction of fluids may be more rigidly enforced. This is even more true of cases presenting a hydremic or even dropsical tendency. The rule, in such instances, is to favor concentration of the blood by not allowing more than 32 ounces of fluid *per diem*. In any given instance in which increasing weakness of the heart, with an impeded circulation, naturally diminishes the excretion of water by the cutaneous and renal routes, the circulatory system must receive unusual and careful attention and the consumption of fluid must be limited. In this form of the affection (anæmic), the appetite is often impaired, and the dietary suited to the needs of the patients is exceedingly difficult to enforce. They often insist upon being allowed to partake of light lunches between meals and on retiring, and the writer endorses such a course. Among the best dishes for the purpose are a cup of hot broth or bouillon with part of a French roll, a glass of milk with a graham wafer, a thin sandwich of scraped-beef or chicken, or the like.

The value of highly nutritious blood-making food—tender meats, milk, eggs, green vegetables, fruits—in this form of obesity is undoubted, and indicated first of all, but the quantity of proteid food must not be excessive. The great difficulty in these cases is to accomplish the decomposition of proteids by muscular exercise, such subjects being lethargic and strongly averse to physical exertion. Fatty food which does not inhibit the disposal of the nitrogenous materials to the same extent as the carbohydrates should be somewhat more restricted even than indicated in the dietary given above. The superior value of this method has received adequate verification from personal experience. A light acid wine, as dry Moselle, Rhine, or claret, in definite quantity—four ounces (120 cc.)—at dinner, is useful.

The Mechanical Treatment.—To increase oxidation by exercise is, next to an appropriate dietary, the most important element. The special form of exercise, and also the duration and frequency, must be carefully adjudged for the individual patient. One of the principal uses of exercise is to maintain an appropriate proportion of albumin in the body, but “not only the fat but organic albumin is likewise used up by muscular activity” (Oertel). Physical exercise also promotes the destruction of the fat already warehoused in the system, and, moreover, it invigorates cardiac action and induces deeper breathing. Muscular exercise, however, should not be too violent, particularly in the cases manifesting circulatory disturbances or evidences of fatty infiltration of the heart. The writer’s best results have been from walking out of doors, later by increasing the pace, and, finally, climbing exercises either at home or at open-air health-resorts, combined with gymnastics for the arms and trunk. Reference was previously made to the “health-paths” when speaking of the treatment of fatty overgrowth. These paths should have an incline ranging between 5° and 20°. The amount of exercise should be measured by the use of a good pedometer.

It is all-important to make the minutest study of the patient’s cardiovascular system, and to observe the effect of the muscular exercise. For example, if the case be one of the anæmic, or hydræmic type, or presents some complication, then the patient must begin with short walks on the level, to be slowly and gradually increased as the force of the heart and strength of the patient permit; and it is desirable to distribute the exercise over both the morning and afternoon hours if this is practicable. On the other hand, in instances of the plethoric form of the affection, a greater amount of physical exercise and even walks up inclines of moderate degree may be taken from the commencement. Strümpell remarks: “In dealing with cases of obesity in which the condition is due less to over-feeding than to lack of muscular exercise, it might be decidedly advisable to lay the most stress upon the increase in muscular activity.” The so-called “resistance exercises,” introduced by the Schotts in the treatment of chronic cardiac diseases, may be employed in the anæmic or hydræmic varieties of obesity in which cardiac dilatation is associated. After marked signs of improvement in the cardiovascular system and the respiratory forces has been brought about, then suitable gymnastics and walking exercises may be substituted. Great care must be exercised in prescribing the mechanical treatment in obese patients who have atheromatous vessels. Complications and intercurrent affections must be relieved by appropriate treatment. When oxidation cannot be sufficiently promoted by muscular exercise, a course of rather deep massage, with a view to increasing the muscular system and stimulating the circulatory and eliminative organs, is the best substitute. With massage the Swedish movements may be combined.

Although to a lesser extent than the muscular exercise, balneotherapy also promotes oxidation. When no contra-indications exist, cold- or salt-water baths followed by active hand-rubbing by the patient himself may be advised. These baths should be brief and the temperature of the water not too low at the start. If gouty manifestations are prominent, hot baths are to be employed preferably, since they increase elimination through the skin, while, on the other hand, cold ablutions tend to increase the suffering

of the patient. Bornstein advises daily hot baths in obesity, as they induce freer elimination through the skin and kidneys. It is important to maintain efficient excretion of the products of combustion by constant attention, not only to the skin, but also to the bowels and kidneys.

The treatment of associated diseases, many of which stand in the relation of cause, is highly important,—more especially gout and rheumatism. It is decidedly inadvisable to institute the usual reduction treatment when gout and obesity are combined, and such a course aggravates the first-named disease. The most brilliant results in such cases are obtained by adapting the treatment principally to the gouty element, although some of the measures employed favorably influence the obesity, *e. g.*, the physical exercise. To rearrange appropriately the dietary for these combined cases is extremely difficult. On the other hand, there are numerous conditions and diseases associated with obesity in which the reduction treatment is called for and should precede. It is well known that diseases of the circulatory system, in particular, are unfavorably influenced by even a moderate degree of corpulency. The same is true to a lesser extent of bronchitis, asthma, and chronic interstitial nephritis.

Medicinal Treatment.—A number of watering-places, particularly Marienbad and Carlsbad, enjoy an enviable reputation for the treatment of obesity. From a therapeutic standpoint, however, a suitable dietary, muscular exercise, and other details, are equally important with the waters ingested. The spas are adapted especially to the plethoric form of the complaint, but not to the anæmic. In the latter form, mild aperient waters, containing iron, are often serviceable. Neither should patients presenting marked cardiovascular disturbances resort to these spas. Such a course of treatment is not to be pursued except under the strict surveillance of a resident practitioner who is competent to arrange an appropriate regimen. Personal observations lead to the inference that the beneficial effects from the spa treatment are rarely permanent. In mild grades of plethoric obesity, such places as Hamburg, Kissingen, Bridesles-Bains, and Vichy, abroad, and Saratoga and Virginia Hot Springs, at home, may be recommended.

On the whole, the medicinal treatment is neither satisfactory nor successful. As stated above, hæmatinics are useful in the anæmic variety. Some of the complicating affections call for special therapeutic agents,—as gout, rheumatism, circulatory disturbances, and the like. Certain remedies recommended in the treatment of this disease are harmful—*e. g.*, phytolacca berry. Thyroid-feeding has come into more or less favor. Leichtenstein, Wendelstadt, Ewald, and others, have reported successful results in a number of instances, especially in those exhibiting the anæmic, flabby, “myxœdematoid” form of obesity. The loss of weight was from 2 to 3 pounds (1 to 1.5 kgm.) in one week, and as high as 20 pounds in two to four weeks. In a number of selected cases belonging to this category the use of thyroid extract (desiccated) in small doses caused a progressive loss of weight without injury to the general health; but it quite as often fails. In the majority this loss is not maintained after the reduction of 10 to 15 pounds has been accomplished. The commencing dose should be small and then slowly and gradually increased, but it is not advisable to exceed gr. v (0.324) thrice daily. It is wise to guard the heart by combining small doses of strychnine or digitalis.

In this connection it should be pointed out that a myxedematous condition is not uncommonly associated with the anæmic form of obesity.¹ Thyroidin, the active principle of the thyroid gland, and iodothylin, give results that are in every way comparable to those of thyroid-feeding, according to Baumann and Ross as well as personal experience. Jeczowski treated 10 cases of corpulence by thyroidin in doses of from 5 to 8 grains (0.3 to 0.5 gm.) *per diem*. In one patient more than 40 pounds (18.1 kgm.) were lost in two months, and in another 30 pounds (13.6 kgm.) in three months. Symptoms of thyroidism—restlessness and tachycardia in particular—are the signal either for a reduction in the dosage of thyroid extract or its temporary withdrawal.

The cathartic mineral waters are indicated in cases in which there has been gormandizing with disturbance of the portal system, and in many cases of plethoric obesity, in the earlier stages, in connection with a suitable restriction of the dietary. When saline laxatives are employed the other fluids must be correspondingly reduced. The heart and blood-vessels must always receive the minutest attention, and any circulatory disturbance must be promptly met; it is often necessary in advanced cases, with or without œdema, to resort to digitalis or strychnine. In a certain proportion of cases the dietetic-mechanical treatment of obesity, even with gradual loss of weight, is attended with marked nervous disturbance, usually assuming the form of restlessness and abnormal excitability. It is important, when such symptoms arise, to carry on the treatment still more slowly, when they may disappear; but, if they do not, then it should be discontinued.

Treatment of Local Obesity.—The best method is a course of local massage combined with a mild general-reduction cure. Allard² recommends the employment of a vibrating ball controlled by an electric motor in circumscribed obesity; this method of treatment has proved efficient in a limited number of cases. When the abdomen is the seat of the localized overfatness it is well to estimate the element of intestinal distention, and gastrectasis, from which such patients commonly suffer, and to direct appropriate measures to these conditions when present. Moreover, the massage exercises a beneficial effect in overcoming the atony of the intestines, thus diminishing the girth measurement.

¹ "Some Respiratory Conditions Dependent Upon Gout and Obesity," by the writer, *The Philadelphia Medical Journal*, October 26, 1901.

² *Revue de therapeutique*, 1905, No. 6, p. 191.

CHAPTER XXXIII.

RICKETS.

By GEORGE F. STILL, M. A., M. D. (CANTAB.), F. R. C. P.

"THE most recent and ordinary name of this disease," wrote Glisson in 1650,¹ "is The Rickets, but who baptised it and upon what occasion and for what reason, or whether by chance or advice it was so named, is very uncertain." Glisson regarded the rickets in his time as "absolutely a new Disease and never described by any of the Ancient or Modern Writers" "It became first known," he says, "about thirty years since in the Counties of Dorset and Somerset lying in the Western part of England." The term "Rachitis" or "Rachites" he suggests as an alternative, not because he thinks that there is any evidence that "Rickets" was a corruption of the Greek term, but because he thinks that "they that are expert in the Greek and Latin tongues may peradventure expect a name from us whereof some reason may be given." The word Rachitis, he explains, was selected by himself and some of his friends because the spine (*ράχis*) was "the first and principal among the parts affected in this evil."

In Germany, the disease has been known as "die Englische Krankheit," a term which must be taken to indicate rather the source of the original description of the disease, than any distinguishing prevalence of rickets in England or among English-speaking people.

Up to recent times, certain conditions were included under the name of rickets which are now believed to be entirely distinct pathologically. The disease which is now called infantile scurvy (Barlow's disease), was formerly described as acute rickets, hemorrhagic rickets, or scurvy rickets; and under the head of foetal rickets was classed the disease which is now known as achondroplasia.

Rickets will be described here under three heads: (1) congenital or foetal rickets, (2) ordinary rickets as seen in the first two or three years of life, and (3) late rickets.

Congenital and late rickets are (in the opinion of most observers) extremely rare; moreover, there is still some doubt whether the conditions described by these names are in all cases identical pathologically with the common rickets of infancy. It will be convenient, therefore, to describe the common form of rickets first, for it is in this form that the characteristics of the disease have been most carefully observed.

Geographical Distribution.—There is a general consensus of opinion that rickets is more prevalent in temperate zones than in very hot or very cold countries, but this vague generalization rests on no

¹Treatise on the Rickets. Transl. *Phil Armin.*, 1651.

firm basis. Statistical evidence is lacking with regard to many parts of the world, and even such statistics as are available are often of little value for purposes of comparison, inasmuch as some observers have failed to state the age limits to which their figures refer, and others have given no indication of the evidence which has been accepted as establishing the presence of rickets. It must be remembered also that statistics have almost always been taken from hospitals or dispensaries and therefore refer only to sick children and to the poorer classes, not to the child population in general.

With these limitations, the following figures may be quoted as indicating, at any rate, the widespread occurrence of rickets:

<i>Place.</i>	<i>Age.</i>	<i>Frequency.</i>	<i>Observer.</i>
New York (Tenements)	1-16 months.	13 out of 67, or 19.4%	Long & Steele (Freeman).
New York (Hospital)	Up to 2 yrs.	60 out of 66, or 91%.	Freeman.
Philadelphia	Up to 5 yrs.	28 per cent.	Parry.
Boston (U. S. A.)	Under 2 yrs.	79.5%	Morse.
Buffalo	Up to 3 yrs. (Italians)	70%.	Snow.
Buffalo	Up to 3 yrs. (other nationalities)	11-12%.	Snow.
London	Up to 3 yrs.	44.6%.	Still.
Manchester	(sick children)	30.3%.	Ritchie.
Edinburgh	Up to 3 yrs.	"Rather more than 50%."	J. Thomson.
Paris	Children	One-third.	Marfan.
Berlin	Up to 3 yrs.	65.8%.	Cohn.
Prague	Up to 5 yrs.	31%.	Ritter.
St. Petersburg	Children (moderate rickets)	60-80%.	Ionkowsky.
Moscow	Children	80%.	Kissel.
Christiania	Up to 3 yrs.	19.9%.	Quisling.
Christiania	Children	32%.	Johannessen.

It is clear that rickets has a wide distribution in the northern hemisphere and, although figures are lacking for the southern hemisphere, the disease is known to be prevalent in Australia, South Africa, and South America. It has been stated that it is almost unknown in the tropics but the accuracy of this statement is doubtful. Recently during a boundary investigation in Africa, cases of severe rickets were seen among the natives of the Gold Coast Colony, 5° to 11° north of the Equator, and rickets is known to be prevalent in the West Indies. It is also believed that in very cold regions, such as Greenland, the disease is very rare. In China, Japan, India and Thibet, rickets is said to be an exceedingly rare disease (Palm); but such statements must be received with caution, for it seems probable that many observers have included only such cases as showed curvature of bones and other symptoms which are only met with in severe degrees of rickets.

Rickets is said to be much more prevalent in moist climates than in dry (Palm), and in low-lying districts than in altitudes: it is said to be rare at an elevation of more than 2,000 feet (about .75 km.) above the sea (Rehn), but both Baginsky and Monti observed rickets to be frequent in places 2,000 to 4,000 feet (.75 to 1.25 km.) above the sea.

It is generally held that rickets is a disease chiefly of cities and large towns and no doubt this view is correct, but in England, certainly, rickets is very common in country districts also, and it seems likely that investigation would show this to be the case in other parts of the world. A collective enquiry by Norwegian physicians showed that in Norway out of 615 cases of rickets, 359 were from towns, 256 from the country; but as no statistics are forthcoming of the relative proportions of town and country child-population, it is difficult to obtain any conclusive evidence as to the relative frequency of rickets in town and country.

Probably the social conditions of town life are of much more importance in the etiology of rickets than any geographical limits. This has been well illustrated by the increase in the frequency of rickets which has been noticed in Melbourne since the great influx of population attracted by its commercial prosperity some fifteen years ago. In 1885, rickets, even in its slightest manifestations, was extremely rare at the Children's Hospital in Melbourne. In 1895, rickets had become quite a common disease. This increase corresponded with an increase of poverty and extended use of cheap artificial food preparations for infant feeding (Snowball).

Season.—Season plays little if any part in the production of rickets, but several observers have noticed a special frequency of rickets among hospital patients during the winter months. This has been attributed to confinement in ill-ventilated rooms, but it is not proved that rickets has its onset more at one time of the year than another and there is an obvious reason why rachitic children should be brought for treatment during the winter months—a large proportion of the rickety children are not brought for rickets, but for respiratory complications and these are much commoner in the cold season than in the warm.

Age and Sex.—The onset of rickets is so insidious that any exact determination of the age at which it begins is usually impossible. It rarely begins after the age of three years, and probably seldom before the age of three months: among hospital out-patients the second year of life shows the largest proportion of rickets. Out of 1,662 cases of rickets, 1,268 were between one and two years old (Comby). Some statistics of consecutive patients under the age of three years taken from the writer's out-patient clinic illustrate the relative frequency at various ages:

	Birth to 3 months	Months 3-6	Months 6-12	Years 1-2	Years 2-3
Rickets	10	10	24	38	18
No Rickets	31	24	22	27	20

It seems probable that there is little, if any, relation to sex. Out of 179 female children in the hospital, 73, that is 40.8 per cent., showed rickets, while out of 138 boys, 57, that is 41.3 per cent., were found to be rickety. According to Woronichin, out of equal numbers of sick children of each sex, the proportion of rachitic boys to rachitic girls was 13 to 10.

Etiology.—Many different views have been held as to the etiology and no doubt several factors may play some part in its production. But it may be said at once that, although there may be several predisposing or contributing causes, the one determining cause is faulty feeding or faulty

assimilation. Rickets is, in fact, a food disorder. Recognizing this, however, we may well pay attention to those other factors to which more or less weight has been attached by various observers, for some of these factors may prove to be of importance in the prophylaxis of the disease.

Overcrowding: Defective Hygiene.—As already mentioned, rickets is more frequent in cities than in country districts and this fact has suggested that defective hygiene is responsible for the disease. In many of the cities where rickets is most prevalent there is much overcrowding, and where a whole family of several children with their parents live in one room, the vitiated atmosphere may well interfere with the nutrition of an infant who spends perhaps the greater part of the day and night in this one room. Undoubtedly, in London, rickets is far commoner among the poorer classes than among the wealthy; but it seems likely that the difference lies much less in environment than in feeding. The children of the well-to-do become rickety when fed in the same way as the children of the poor. The very minor part played by environment seems to be shown also by the fact that, in London at any rate, rickets is usually treated amongst hospital patients by simple dietetic measures and the administration of cod-liver oil, with no change of environment; and yet the results of such treatment are excellent.

The same objections might be urged against the view which has been held that deficiency of sunlight is a large factor in the causation of rickets. It is pointed out that in cities, with their narrow streets and high buildings, the rooms of the poor are often ill-lighted and get little or no sunshine. But it is equally true that in some less-civilized parts of the world, where rickets is said to be extremely rare, it is customary to live in dwellings even less open to sunlight.

If, however, there is little evidence that overcrowding and squalor, with their attendant defects of sanitation, have much influence *per se* in the production of rickets, clinical experience seems to indicate strongly that certain conditions of city and town life do play a very important part in determining its prevalence. The struggle for existence in these crowded districts often makes it necessary that both parents should go out to work, and infants are therefore artificially fed; moreover, wherever poverty abounds, the cheaper substitutes for cow's milk are likely to be used, especially condensed milk. It seems probable also that, particularly amongst town-bred women, there is an increasing inability to suckle their offspring, which favors the occurrence of rickets.

Parental Influence.—Direct heredity has been held accountable by some (Hench, Pfeiffer, Ritter von Rittershain). Ritter found traces of rickets in the mothers of 27 out of 71 rickety children. But in the districts from which observations on this point have come, rickets is a common disease, and it is at least possible that parent and child have both been subjected in early life to faulty methods of feeding.

The health of the mother during pregnancy has long been considered to have some influence upon the development of rickets in post-natal life. Jenner, discussing this point, said: "Of this much I am sure, that, when the mother is in delicate health, in a state of which anæmia and general want of power form the prominent features without being the subject of disease, usually so-called, there the children are often in a very decided degree rickety, although the father is in robust health and the hygienic

conditions in which the children are placed, most favorable." Phthisis during pregnancy is especially mentioned by Garrod and Fletcher¹ as a cause of rickets in the offspring, and the same writers consider that want of fresh air and exercise during pregnancy has a similar result; they mention, also, multiple pregnancy, and pregnancy at an advanced age, or at an unduly early age, as factors.

It is commonly stated that the last children born in a large family are more often affected with rickets than the earlier children, especially if the pregnancies have been not only numerous but in rapid succession. In such cases it is supposed that exhaustion of the mother interferes with the nutrition of the infant in some way so that some months after birth rickets appears. Actual statistics hardly bear out this supposition. Baxter² found that in consecutive cases of rickets, 19 per cent. were first-born, 13.5 per cent. second-born, 19 per cent. third-born, 13.5 per cent. fifth-born, 8 per cent. sixth-born, 16 per cent. seventh-born, 2 per cent. ninth-born or later. Similar in its effect, presumably, is lactation during pregnancy, which some observers have thought to be a cause of rickets in the offspring.

Whether any of these influences can be regarded as more than predisposing, is doubtful. Rickets at birth is generally thought to be exceedingly rare, and when the disease makes its appearance some months after birth, there is always a possibility and often a probability that post-natal factors, particularly the feeding, played a larger part in producing the disease than any parental influence before birth.

Syphilis.—Parrot's view that syphilis causes rickets is now generally discredited; but some still hold that syphilis strongly predisposes to rickets. Monti states that he has never seen a case of inherited syphilis which did not develop rickets; Cheadle, on the other hand, says that many cases of congenital syphilis are not rickety. Undoubtedly, some of the most severe degrees of rickets are seen where this disease is associated with congenital syphilis, and it would seem that in such cases the osseous and perhaps the visceral lesions of rickets may be modified not only in degree but also in kind. In the skull, osteophytic change is more common and more marked when syphilis is associated with rickets although it may occur with rickets alone. Some have thought also that localized thinning of the cranial bones, craniotabes, is specially frequent when these two diseases are combined.

Dietetic Causes.—What part, if any, is played by the factors already mentioned is uncertain; but there are strong grounds for believing that dietetic influences stand in a much more direct relation than any of the foregoing. Put briefly, the facts are these: Rickets is uncommon and in its severer degrees is exceedingly rare in infants who are having the breast milk only. It occurs almost invariably where the feeding has been such that the food constituents depart widely from the standard of human milk or include excess of carbohydrate whether in the form of sugar or starch. Rickets occurs in some of the lower animals, and in these it has been shown to be preventable by simple dietetic measures. Several observers claim to have produced changes resembling rickets in animals by special methods of feeding. Rickets in chil-

¹*British Medical Journal*, September 21, 1895.

²*Pathological Society Transactions*, vol. xxxii, p. 360.

dren is successfully treated by suitable feeding without other measures of any sort.

As to the particular fault in the diet, some indication is obtained by a comparison of the methods of feeding in a series of rachitic children. These can be grouped thus in approximate order of frequency: (1) Starchy food; corn flour; potato; bread with more or less milk, fresh or condensed. (2) Condensed milk alone, often excessively diluted. (3) Proprietary foods, whether containing starch or not, and made with or without the addition of fresh milk. (4) Cow's milk diluted, without addition of cream. (5) Breast milk, with addition of starchy foods. (6) Breast milk only.

Great importance has been attached to the early use or to excess of carbohydrate food, especially starch. Baxter found that 92 per cent. of the cases of rickets had had farinaceous food before the age of twelve months, 42 per cent. had had farinaceous food daily from their birth, 30 per cent. daily from the age of three months, 4 per cent. from the age of six months, and 16 per cent. from the age of nine months. He found, also, that in many, though not in all, the first onset of the disease and its degree of severity appeared to be distinctly related to the period at which the administration of starchy matter was begun and to the proportion between this element in the dietary and the others with which it was associated.

It is clear, however, from the occurrence of rickets in groups 2, 4 and 6, that the use of starchy food is not essential to its production. There is also some evidence that excess of sugar is not an essential factor, for in group 2 personal observations showed that rickets most often arose where excessive dilution of the condensed milk had been used so that the proportion of sugar was actually slightly below that present in human milk; and in group 6 it is very improbable that any notable and prolonged excess of sugar should occur; for the average proportion of sugar in human milk is remarkably constant.

From the occurrence of rickets on a diet of condensed milk in watery dilution, it may be conjectured that the fault is one of defect rather than of excess, for all the constituents of milk in such feeding are usually present in unduly low proportion; moreover, compared with human milk this dilution of condensed milk will show a relatively greater defect of fat than of proteid, as can be seen from the following comparison:

	<i>Human milk.</i>	<i>Condensed milk as often given (about 1 in 10).</i>
Proteid	2.0 . . .	1.0 per cent.
Fat	3.59 per cent.
Sugar	7.0 . . .	5.4 per cent.
Salts22 per cent.
Water	87.3 . . .	92.5 per cent.

Analyses of human milk make it probable that deficiency of fat is commoner than deficiency of proteid. Where rickets occurs in an infant who has been fed only on cow's milk diluted, there has almost always been dilution sufficient to reduce the fat to half or less than half the proportion present in human milk, and this low proportion has been continued usually for many months. Such dilution reduces the proteid little if at

all below that found in human milk. When the proprietary foods are used, whether with fresh milk or without, analysis shows that there is almost invariably a deficient proportion of fat in the diet. All these facts suggest that deficiency of fat in the food is an important factor.

Failure of assimilation of fat may be as effectual as deficiency of fat-supply in causing fat-starvation. It seems likely that an infant, even when receiving an ample quantity of good breast milk, may fail to assimilate it properly if farinaceous food is being given at the same time. Whether starchy food or excess of sugar has any special influence in hindering the absorption of fat is uncertain, but there is no doubt that by setting up dyspepsia and fermentation it can and does interfere with the absorption of any food-stuff, including fats. Similarly, any cause which weakens the infant's digestive powers, be it simple debility, as in a premature child or in one of twins, or a gastro-intestinal disorder, or disease such as syphilis or tuberculosis, may interfere with the absorption of food and so of the fat.

Strong support has been given to this view by the observations of Bland Sutton upon animals in the Zoölogical Gardens in London. These have been described very fully by Cheadle,¹ from whose account the following statements are quoted: "Young monkeys deprived of their mothers' milk and fed entirely upon vegetable food, chiefly fruits, became rickety. Two young bears fed exclusively upon rice, biscuits, and raw meat, of which latter they hardly ate, died of extreme rickets. For many years the lion whelps were weaned early and fed on raw flesh only; they invariably became rickety and died. When milk, pounded bones, and cod-liver oil, were added to the raw meat, they lost all signs of rickets and were successfully reared." Here evidently there had been no deficiency of proteid. The addition of pounded bone to the diet makes the experiment less conclusive than it might have been if fat only had been added; but a comparison with the results of addition of cod-liver oil only to the regimen of children makes it all but certain that the fat was the effective therapeutic agent.

The value of cod-liver oil is in itself suggestive of the role of fat-starvation and from recent experience it would seem that any fat, animal or vegetable, provided it is easily digested, is equally curative of rickets. It is noteworthy also that those who have advocated the use of phosphorus have almost always used it in an oily solution.

Whilst, therefore, it seems possible that deficiency of proteid, and perhaps deficiency of certain salts, in the food may contribute in some degree to the production of rickets, there is strong evidence that the chief, perhaps the only constant, fault is deficiency of fat assimilation, whether this deficiency be due to a low proportion of fat in the diet, or to faulty methods of feeding interfering with digestion and so with the absorption of fat. It must be added, however, that some experiments on pigs, by Herter, of New York, showed that prolonged fat-starvation, although it produced muscular weakness and drowsiness, did not produce the bone-changes of rickets (Freeman).

Pathology.—Morbidity Anatomy.—The most obvious change is the enlargement at the junction of epiphysis and diaphysis in the ribs and in the long bones, but to understand the changes here, it is necessary to have

¹ *Allbutt's System of Medicine*, vol. iii, p. 131.

some knowledge of the normal processes of growth in bone. At the ends of the long bones, for instance of the radius of an infant about nine months old, there are between the cartilage of the epiphysis and the cancellous tissue of the diaphysis, two distinct zones of transition: the one nearer the cartilage is a thin, translucent, bluish-gray band about $\frac{1}{16}$ to $\frac{1}{10}$ of an inch (1 to 2 mm.) in thickness, and beyond this is a much narrower yellowish-white opaque zone which, toward the cartilage, has a sharply defined and perfectly regular limit, but toward the bone merges irregularly into the cancellous tissue: the former is the zone of proliferation, the latter is the zone of calcification.

In rickets, the bluish-gray zone of proliferation is enlarged so that it may be more than twice the normal thickness, and instead of being an even band with sharply defined edges limiting it from the cartilage on the one side and the zone of calcification on the other, it is quite irregular, especially toward the zone of calcification, where, even with the naked eye, it can be seen that the two zones are mixed together, islets of calcification are seen amidst translucent cartilage, and irregular processes of cartilage extending into the region of calcification, and the whole is abnormally vascular so that to the naked eye, numerous vessels are obvious, traversing these confused zones in all directions.

Histologically, there is the same confusion; the cartilage cells are more numerous than they should be, the arrangement of columns has lost its regularity; they are ill-formed and no longer parallel. Between them in many places are areas of calcification, sometimes even of fully formed laminated bone, lying amid cartilage cells and cartilaginous matrix in which are numerous vessels passing inward from the adjacent periosteum or perichondrium. The cancellous tissue of the shaft has also an undue vascularity, and the absorption of this tissue which should proceed but slowly, keeping pace with the formation of new bone from the periosteum without, proceeds in rickets too rapidly, so that the bone consisting of an imperfectly ossified layer without, is further weakened by the rarefaction and looseness of its cancellous tissue within.

The subperiosteal formation of bone is also disturbed, the periosteum itself becomes thickened and the proliferating layer beneath, in which calcification should occur, is excessively vascular, and contains abundant cell elements, but is imperfectly calcified, and the production of true laminated bone is deficient, so that the bone here also is softer than normal and bending easily occurs. The bone thus formed may be of spongy character, a condition specially noticeable in the thickened areas of the parietal and frontal bones, where also the vascularity is sometimes so great that it can be observed clinically as a bluish discoloration seen through the tense scalp.

Muscles.—It is stated that the muscles show microscopically some blurring of striation, and that there is excess of fat in the connective tissue between the muscle fibers. In severe cases, fatty degeneration of the muscle fibers themselves has been observed.

Viscera.—The liver is sometimes enlarged, and the cause of this is not yet certain. The surface is smooth; the consistence is not appreciably altered. It is stated that the interstitial tissue is chiefly increased, that in the portal areas particularly, there is some overgrowth of connective tissue, and some increase of the liver cells (Dickinson). Jenner

described an "albuminoid" change which, whilst giving to the liver some of the translucency of lardaceous disease, differs in not yielding the iodine reaction. But the connection of such changes with rickets is quite uncertain. A much commoner change is fatty infiltration, but this certainly is not peculiar to rickets.

The Spleen.—The spleen is only occasionally found, at autopsy, to be enlarged, and then only to a slight degree. This, like the enlargement of the liver, has been attributed by some to overgrowth of the fibrous stroma, by others, to increase of the cell elements. According to recent observations, the first change is hyperplasia of the spleen-pulp; then overgrowth of the perivascular connective tissue and of the stroma in general, and ultimately in severe cases, replacement of the parenchyma by fibrous tissue, so that the Malpighian corpuscles atrophy (Sarcinelli, Sasuchin).

The Brain.—The brain has been described as hypertrophied, and it is suggested that this is due to increase of neuroglia, but this has not been established. It was formerly supposed that hydrocephalus was a result of rickets. V. Starek states that in 113 autopsies on rickets, he found hydrocephalus 12 times. Such an experience must be very exceptional; probably any association between rickets and hydrocephalus is nothing more than a coincidence; but Stoeltzner, whilst denying any causal connection between rickets and progressive hydrocephalus, states that a slight dilatation of the ventricles, insufficient to produce any untoward symptoms clinically, is a characteristic feature in the morbid anatomy of rickets; the writer is unable to confirm this from his own experience.

The lungs show no characteristic change, but there is almost always much collapse of alveoli, and more or less bronchitis and bronchopneumonia. These may be regarded as epiphenomena; they show no peculiarities to distinguish their occurrence from that in any other diseases.

Pathogeny.—Chemistry of Rickets.—The chemical pathology is at present entirely unknown. Of the several theories which have been put forward, none rests upon a satisfactory basis; experiments and observations have been discordant and contradictory. The facts which have to be explained are not merely the softening and bending of bone, but the overgrowth of cartilage, the perversion of the whole process of bone formation, and in addition more general disturbance, especially in the nervous system, and also in the muscles and viscera. There is evidently some wide disturbance of metabolism.

One of the few points upon which there is agreement is deficiency of lime-salts in the bones: in the healthy child the bone yields about 63 to 65 per cent. of earthy salts, and 35 to 37 per cent. of organic matter; in rickets, according to Friedleben, the tibia yielded 37 to 48 per cent. earthy salts and 51 to 63 per cent. organic matter: other observations showed in rachitic bone, 20.89 per cent. earthy salts, 79.1 per cent. organic matter (Boettger), 20.6 per cent. earthy salts, 79.4 per cent. organic matter (Marchand). Deficiency of lime in the food was found by Chossat (1842) to produce fragility of bones in pigeons, and recently Stoeltzner, by feeding puppies on lime-deficient food, produced softening of bones; but mere softening or fragility of bones is not rickets, and it has been shown both by Friedleben and by Stoeltzner that the changes produced in these experiments are not those characteristic of rickets.

Deficient absorption of lime-salts has also been suggested, but if this were so the lime-salts eliminated in the urine might be expected to be increased; some observers have found this to be the case, others have found no difference from normal urine.

Cow's milk contains .15 per cent. of lime, whereas human milk contains only .02 per cent. of lime (Cautley); it is evident, therefore, that even when cow's milk is given greatly diluted, much more lime is supplied to the child than when breast milk is used: but rickets is very much commoner in children fed on cow's milk than in children who are being fed only on breast milk. The facts that lime-water has no therapeutic value in rickets, and that rickets is so common in districts where the water contains much lime, are also noteworthy, but it is possible that for the absorption of lime, its administration in organic combination may be important.

A relative deficiency of lime, rather than an absolute, has been suggested by Kassowitz, who points out that prolonged hyperæmia of bone, which he produced by intermittent constriction of the limb of a growing animal, causes proliferation of cartilage and some absorption of bone; the formation of bone tissue is in excess, the supply of lime salts necessary for its perfect calcification is not correspondingly increased. This theory presupposes some irritant chemical or otherwise, which causes prolonged hyperæmia and changes similar to those of chronic inflammation in the areas of bone-formation. No such irritant is known to exist in rickets, but the frequent association of gastro-intestinal disturbance with this disease has led some to suggest that this may be primary, while the rickets is the result of an intestinal toxæmia.

Solution of lime salts by lactic acid circulating in the blood has also been suggested; according to this view, lime already deposited in the bone is dissolved out by the acid, or the acid in the blood prevents the deposit of lime salts. This theory is based on the fact that starchy food is liable to give rise to fermentation in the alimentary canal with the production of lactic acid, and that starchy food is known to be frequently associated with the presence of rickets. Lactic acid has been found in the urine in rickets. It has been stated that lime salts are found in excess in the urine; and finally Heitzmann claimed to have produced true rickets by administering lactic acid to animals in their food. Such a theory, however, is untenable. It has been shown that the alkalinity of the blood is not diminished in rickets (Stoeltzner)—injections of lactic acid into animals and also a repetition of Heitzmann's experiments, failed to produce rickets (Spellman). A diet of meat, which does not produce lactic acid, produced rickets in animals (Guérin). The addition to the diet of certain nutritive elements in which it is deficient, cures rickets without any diminution of the farinaceous constituents (Cheadle). Lactic acid is often found in urine apart from rickets; in some cases of rickets there is no excess of lime in the urine (Zuelzer).

Excess of carbonic acid in the blood has been held accountable (Wachsmuth) by keeping the lime salts in solution: the only clinical evidence adduced in support of this theory has been the occurrence of rickets in children living in ill-ventilated rooms; but rickets occurs both in children and in animals who spend a large part of their time in the open air. The disease is successfully treated without any change beyond dietetic measures and the administration of oils. Moreover, there is no

proof that any such excess of carbonic acid as could interfere with deposit of lime salts, exists in the blood in rickets. Rickets has been attributed to deficiency of phosphoric acid in the diet, especially where calcium is deficient at the same time: on the other hand the administration of phosphate of potash to dogs has been stated to produce rickets (Delcourt) and Wegner has stated that by administering phosphorus to animals, who at the same time were deprived of lime-containing food, he produced rachitic lesions. The same observer found that by injections of phosphorus near the epiphysis of growing animals, he produced a change in the bone of inflammatory type. But none of these observations can be considered as established, and although Wegner's conclusion that rickets is the result of the combined action of some irritant on growing bone and of a deficient supply of lime, may be correct, his experiments hardly prove it.

Some experiments have recently been made by Freund on the relation between fat in the diet and the absorption of phosphorus from the food. He found that when infants were fed upon a diet of cream diluted with water so as to contain more fat than the diet of other infants who were fed on milk diluted with water, the urine contained a much larger proportion of phosphates and from this fact and other results of his investigations, he concludes that when much fat is given in the food, there is a much greater absorption of phosphorus compounds from the intestine. Possibly this observation, taken in conjunction with an analysis of the feces in rickets quoted by Ritter, in which it appeared that a very high proportion of phosphorus compounds, especially calcium phosphate, were excreted in the feces, *i. e.*, were not absorbed from the food in rickets, may serve to connect the clinical facts as regards the deficiency of fat in the ricket-producing diet, and the therapeutic value of fat, with the pathological fact of deficiency of calcium phosphate in the bones.

The problem is obviously extremely complex and no mere chemical formula is likely to explain a condition which is intimately bound up with biological processes of which at present we know but little.

Bacteriology.—There is little to be said in favor of an infective origin. Mircoli, on grounds of theory and experiment, has suggested that the bony changes are of the nature of an attenuated and chronic form of osteomyelitis, and that this is produced by streptococci and staphylococci, which reach the tissues from the alimentary canal. Morpurgo claims to have produced rickets by injecting a certain diplococcus into young rats. Spellman inoculated animals with pieces of bone from rachitic infants and also with the diarrhœal stools of rachitic infants, but in 127 of these and other similar observations, only once found any rickets (Freeman). Up to the present it cannot be said that there is any proof that rickets is ever produced by bacterial infection.

Symptoms.—Rickets is a disorder of nutrition, and, as such, affects the whole organism. The bone changes are only part of a general disease. Much of the confusion as to the pathogeny and even the diagnosis has resulted from the tendency to concentrate attention upon the osseous lesions to the exclusion of other features. A child may suffer severely and yet show so slight a degree of rachitic change in the bones that the disease might almost pass unnoticed if only the osseous system were considered. The stress may fall upon the nervous system in one case,

upon the muscular in another, and perhaps even upon the blood and blood-forming tissues in a third.

Before describing the symptoms in detail, an outline of a typical and well-marked case of rickets may be given. An infant aged about eighteen months is brought for inability to walk. He has been suckled entirely perhaps for six or seven months, and then has had condensed milk and occasionally bread or potato. For some months past, he has sweated profusely about the head and neck whenever he falls asleep. Dentition did not begin until he was nearly a year old, and even now he has but three or four teeth. He has never walked, and sitting on the mother's lap there is a marked kyphosis especially in the upper lumbar region. He is pale and fretful; perhaps rather fat, but flabby; the head is unduly large, with a tendency to squareness; the anterior fontanelle is much more widely open than it should be at this age. The chest is ill shaped, the sternum a little prominent, and there is some transverse constriction below the level of the nipples. A row of knob-like eminences mark the junctions of the costal cartilages with the ribs on each side of the chest; the lower ribs are somewhat everted above the big abdomen, in which the liver can easily be felt, and the spleen is also just palpable. The muscles feel flabby and soft. Just above the ankle and the wrist, the bones seem thickened. There is little or no abnormal curvature of the bones.

Such is a moderate degree of rickets; but there are many more in which the symptoms are altogether less marked, and perhaps delay of dentition and of closure of the fontanelle, with slight thickening at the costochondral junctions (beading of the ribs), and possibly, but not necessarily, some enlargement of the radial epiphysis, are the only evidences of the disease. There are also cases, much less frequent, in which the symptoms are altogether more severe, the limbs are deformed by various bendings and distortions of the bones, the cranium is irregularly thickened or thinned, and the child perhaps shows severe nervous symptoms, convulsions, or laryngismus stridulus.

Nutrition.—The child is often unduly fat especially in slight, or moderate degrees of rickets. This deposit of fat is apparently derived from carbohydrate food, for it is seen where the diet is greatly deficient in fat. It would seem also that this stored fat is unable to replace the functions of fat taken as such in the food. In severe rickets wasting of greater or less degree is common.

Head Sweating.—This is often one of the earliest symptoms and may be so profuse that the pillow is soaked. It usually occurs when the child falls asleep; it is not present in all cases. Probably with this is associated a feeling of heat, for the infant at this stage is very apt to push the bed-clothes off at night and lies uncovered.

Temperature.—This is normal in most cases even during the most active stage of the disease, so far as the writer's observations go; a rise of temperature is almost always due to some complication.

Teeth.—Delayed dentition is one of the most constant symptoms. In 32 out of 42 consecutive cases, between nine months and three years old, this was present. Frequently no teeth have appeared at the end of the first year. Rarely their appearance is delayed beyond the age of eighteen months. There is a striking tendency to very early caries; even before the tooth is fully cut the enamel at the cutting edge is often com-

pletely destroyed. If dentition has begun before the onset of rickets, it is often arrested for several months.

Muscular Weakness: Laxity of Ligaments.—Muscular weakness is a very common result in the active stage of the disease, and in the more severe cases is almost always well marked. It may be quite out of proportion to the osseous changes, and for this reason is liable to be mistaken for some paralysis of nervous origin; it may be so great that a child of two or three years is unable to stand or even to sit up. The late acquirement of sitting, standing, and walking, is chiefly due to this weakness, though in part, no doubt, to laxity of ligaments, and to bone changes. The child who has already begun to stand often loses this power at the onset, so that he is said to have “gone off his legs.” The stooping of the back, or *kypnosis*, which is common in rachitic children, would seem to depend chiefly upon weakness of the muscles of the back. It is possible that muscular weakness of the respiratory muscles plays some part in the tendency to pulmonary affections.

The effects of muscular weakness are intensified by laxity of the ligaments, apparently as the result of some structural change which has not yet been determined, but which renders them soft and yielding. The child can often place his toes behind the ears without difficulty; and the head of the tibia shows an undue amount of lateral mobility, so that it can be loosely knocked against the condyles of the femur. Both these changes, the muscular and the ligamentous, contribute to some of the deformities, such as *talipes valgus* and *planus*, *genu valgum* and *varum*, and lateral curvature of the spine.

Osseous Symptoms.—These are the outcome of the delayed and imperfect ossification, hyperplasia, and abnormal absorption of bone tissue. The most frequent manifestation is the so-called “rickety rosary,” or beading of the ribs, a thickening at the costochondral junction which in a thin child can be seen and in others easily felt. These beads are usually largest and most readily felt on the fifth, sixth and seventh ribs, and in a mild case may be scarcely perceptible on other ribs. They are often seen postmortem to be more marked on the internal than on the external surface of the thorax (Fig. 69). The internal bead, however, is sometimes exaggerated by a displacement of the bony rib backward at the costochondral junction, so that, instead of joining the cartilage end to end, it joins it at an angle which projects on the inner aspect of the thorax (Fig. 70). In such cases the external beading may be obscured altogether, and the junction of rib and cartilage forms a depression externally, so that, clinically, beading may not be detected.

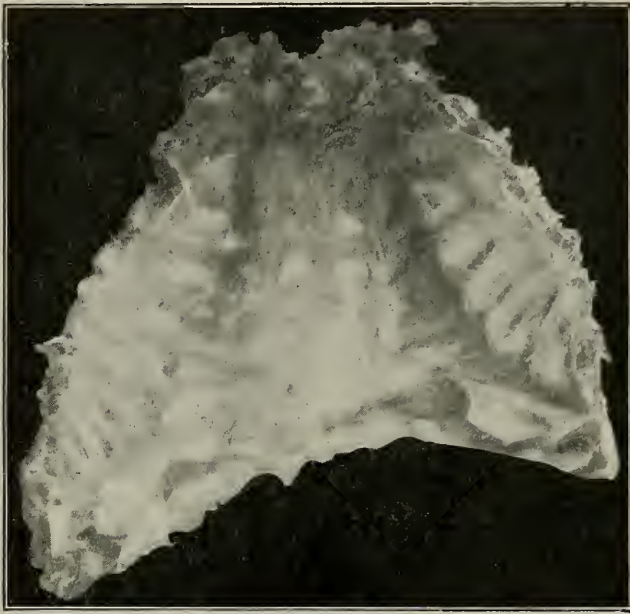
The rickety rosary is one of the earliest symptoms and is often the only bone change to be found during life. It gradually diminishes after the fourth and fifth year and has usually disappeared before puberty.

As a result of the backward displacement of the anterior portion of the rib, in some cases there is an exaggeration of the angle of the rib, posteriorly, or actually a greenstick fracture at that situation; the projections formed thus are sometimes described as “posterior beading,” but are obviously different in their pathology from the anterior “rickety rosary.”

Enlargement of epiphyses is a very common symptom. It is generally most marked at the lower end of the radius, where some thickening was present in 64 per cent. of the writer's cases. At the lower end of the femur

and tibia it is also frequent. Other long bones show it less frequently. The ends of the phalanges of the fingers are occasionally affected giving a somewhat spindle-shaped appearance. Some thickening of the diaphysis of the phalanges has also been described (Koplik).

FIG. 69.



Anterior wall of thorax, internal surface showing extreme rickety deformity; sternum and cartilages project forward in front of the internal beading which is seen to consist partly of a sharply angular junction between bony rib and cartilage.

Owing to the softness of the bones, some degree of curvature in the limbs is common: 43 per cent. of the writer's patients showed curvature of the bones either in the upper or in the lower limbs, but in most of these the bending was slight in degree. The commonest deformity of this kind is a bending outward of the lower third of the tibia,—sometimes there is combined with this, or alone, a forward bend which may be slight or may be sharply angular in the lower third. (Fig. 71.)

The femur is less often affected; it shows a general outward curve in children who are already able to stand or walk when the rickets affects them. In children who are being carried about on the nurse's arm, the curve in the femur is often anteroposterior with the convexity forward. A much rarer result of rickets is the condition known as "*coxa vara*," in which the head of the femur is bent downward so that it is at the same level with, or even lower than, the great trochanter, while the neck of the femur is curved with the convexity forward and upward. Bending of the bones of the upper limbs takes place chiefly in children who spend much of their time crawling about or in the sitting position supporting the weight of the trunk partly upon the hands; a favorite position is that shown in

the illustration (Fig. 72), where the child sits tailor-wise and uses its hands as a prop. Both the humerus and the bones of the forearm are usually curved outward in such cases.

The clavicle, in severe cases, often shows a sharp angular bend forward

FIG. 70.



Anteroposterior section of costochondral junction to show rachitic displacement. In the upper specimen the displacement is slight, in the lower, which was taken from the chest shown in Fig. 69, there is complete displacement.

and upward at the junction of the inner and middle third; and sometimes there is evident thickening here, the result of a greenstick fracture.

All these deformities are the result partly of pressure from without, partly of the weight of the body, and partly of muscular traction upon the softened bones.

Similar in their production are the rachitic deformities of the thorax and pelvis. The former shows a lateral contraction so that the sternum and costal cartilage appear to project forward in front of the ribs, while the depression at the junction of each rib and cartilage forms a furrow passing downward and outward and usually lost in a deeper transverse groove just below the level of the nipple, the so-called "Harrison's sulcus." This sulcus, which extends from the ensiform cartilage to the posterior axillary line, is commonly associated with eversion of the lower ribs over a distended abdomen which increases the distorted appearance of the chest. The pigeon chest (*pectus carinatum*) in which the ribs appear straightened as they pass from the posterior axilla to join the prominent sternum so that the cross-section of the thorax would be roughly triangular with the apex at the sternum, is often described among rachitic deformities. Neither pigeon chest, however, nor "Harrison's sulcus" are essentially rachitic. They are seen in any condition in which there is obstructed respiration.

FIG. 71.



Photograph of a cast at the museum of the Hospital for Sick Children, Great Ormond Street, London, showing a common rachitic curvature of tibia.

Pelvic deformities hardly enter into the clinical picture of rickets in childhood, for they attract no attention at that age, although in the adult female they become of great importance. Rickets here, as in the rest of the bones, may arrest development so that the pelvis remains small and generally contracted. Often there is in addition flattening of the pelvis antero-posteriorly; it is shallow, and, occasionally, from traction of the muscles and the pressure transmitted from the spine and from the femora, more marked distortion takes place.

FIG. 72.



Common position of rickety child with bending of forearm, showing also large head, large abdomen and deformed thorax with Harrison's sulcus.

The bones in rickets become not only soft but brittle, so that fractures, usually of greenstick character, are apt to occur in severe cases with little evidence of traumatism, sometimes apparently from muscular traction alone. This tendency depends partly on absorption of cancellous tissue in the rickety bone, partly on deficient calcification, and partly perhaps upon some abnormal arrangement of the trabeculae in the substance.

As a result of the epiphyseal affection and of the sclerosis which may occur in the bones after the rachitic process has ceased to be active, permanent stunting of growth occasionally takes place, so that the child may be undergrown or actually dwarfed for the rest of its life.

Cranium.—One of the most constant symptoms is delay in the closure of the anterior fontanelle. Normally this should measure about $\frac{3}{4}$ to 1 inch (2 to 2.5 cm.) antero-posteriorly and transversely at the end of the

first year and should close at or about the age of eighteen months. In rickets, it often measures 2 inches (5 cm.) in both directions at twelve months, and is frequently open as late as two and a half or three years; the writer found it open at four and one-half years. This delay of closure is not due to any general expansion of the skull such as occurs in hydrocephalus, for it occurs equally where there is no enlargement of the head and where the head is, as often happens in rickets, unduly large; it indicates rather the general backwardness in bone formation which is one of the features of the disease and which may determine more extensive failure of consolidation in the cranium so that the interparietal and the parietoöccipital sutures are not firmly united for many months.

The size of the head is commonly above the normal; in 17 cases of rickets with an average age of 4.72 years, Lucas¹ found that the average circumference was 21.2 inches (54 cm.), whereas in 17 non-rachitic children with an average age of 6.05 years, the average circumference was 19.95 inches (50.5 cm.). The cause of this increase in size is uncertain; sometimes the brain has been found above the average weight and in some cases there is considerable thickening of the bones of the skull, though hardly sufficient to account for the large size.

The rachitic skull differs from the normal not only in size but also in shape. Two types may be recognized. In the one, the more frequent, the skull is flattened on the vertex and tending to squareness, the posterior segment especially is enlarged; in the other the head is narrow from side to side and elongated antero-posteriorly.

The softening of the bones is shown in the skull by the deep grooves which are hollowed out on its surface by the veins of the scalp so that their course can easily be traced by running one's finger-nail along the groove.

The relation of bossing of the skull and of craniotabes to rickets has been much disputed. Both have been attributed to syphilis by some, and to rickets by others. So far as personal observations go, both seem to occur in rickets apart from syphilis but to be aggravated when syphilis is added to rickets. Some have thought that the symmetrical bosses which occur on the frontal and parietal bones, giving rise to the "*caput quadratum*" or "*hot-cross-bun head*," can be distinguished by their position from those of syphilis, which are said to be closer to the anterior fontanelle. However this may be, there are certainly two conditions, very different in appearance, which give rise to the local thickenings felt on the skull. In the one, the surface of the bone is smooth and the thickening is due to a very vascular increase of the cancellous tissue between the compact inner and outer tables; in the other, there is a deposit of vascular spongy bone on the outer surface of the skull, which has a roughened, worm-eaten appearance. Whether these represent different stages of one and the same process or whether they indicate different processes is at present uncertain.

The term "craniotabes" is used with varying significance. Some would apply it to a diffuse yielding of bone near the sutures, especially about the parietoöccipital sutures, which is not uncommon in rachitic children under twelve months of age and is exceedingly common in infants during

¹ *Pathological Society Transactions*, Vol. xxxii, p. 359.

the first two months of life. In early infancy this thinness of the bone is often associated with unusual separation of sutures and patency of the fontanelles, posterior and lateral as well as anterior. It is very doubtful whether such a condition should be taken as necessarily indicating rickets; certainly it is quite common during the first three or four months of life in breast-fed infants, particularly those of small size and generally feeble development, with no other evidence whatever of rickets.

Much more significant are localized patches of thinning of the bone situated generally in the occipital or in the parietal bone (more commonly the latter) near to, but not actually adjoining, the parietooccipital suture, from which they are separated by an area of firm bone (Fig. 73). The patches are usually about $\frac{1}{2}$ to 1 inch (1.5 to 2.5 cm.) in diameter, round or oval, and can be detected by taking the head between the palms of the hands so that the fingers rest on the posterior parietal and occipital region. On pressing firmly with the fingers, the affected areas are felt to yield, bulging inward like a piece of thick parchment and rebounding when pressure is removed. In severe cases these areas run together, but even then the irregular and patchy distribution distinguishes them usually from the diffuse thinness mentioned above.

FIG. 73.



Posterior view of rachitic skull, showing characteristic areas of true craniotabes.

This condition, unlike the diffuse thinness of the edge of the bone, is often found when the sutures are well closed and only the anterior fontanelle remains patent. It occurs often in the second year of life in children who have only developed rickets after the skull bones are already well ossified. It is an absorption of already formed bone, not a mere delay of development as the diffuse thinness with patent sutures probably is in some cases.

According to the meaning attached to craniotabes, its frequency has varied in statistics. According to some recent observations made by S. Fraser upon children under three years of age at the Children's Hospital, Great Ormond street, London, 29 per cent. of the rickety children showed craniotabes, but this series included many cases in which there was only yielding of the bones near the sutures.

There can be no doubt that craniotabes occurs with rickets without syphilis. In the form of isolated patches it is associated particularly with laryngismus stridulus and tetany, the former of which, if not also the latter, when it occurs in childhood, occurs almost exclusively in the rachitic and has no connection with syphilis. Out of 21 cases of laryngismus stridulus in which the writer noted this point, craniotabes was present in 7. According to Barlow and Lees, 47 per cent. of cases of craniotabes show evidence of syphilis; but many of their cases with syphilis had rickets.

Nervous Symptoms.—Mental.—The rickety infant is often fretful and peevish, but perhaps more from the discomfort of prolonged ill-feeding than from any direct effect of the disease. In later childhood, rickets

has been described as a cause of precocity, and the large head has been supposed to allow a larger capacity for mental development. Thackeray has been quoted as an instance. The accuracy of these observations is very questionable; the child who is invalidated by any chronic disease is likely to be much with its elders and to acquire a precocious manner in consequence. The writer is quite unable from his own observation to affirm any intellectual superiority in rachitic children. There is no evidence that they are inferior, although it was stated by Sir W. Jenner¹ that "Children, the subjects of extreme rickets, are almost always deficient in intellectual capacity and power."

Convulsive conditions are the chief evidence of rickets affecting the nervous system: from about the sixth to the twenty-fourth month convulsions in infancy are most often due to it. The cortex is in some way rendered so unstable that trivial exciting causes, such as constipation or dentition, are sufficient to induce an attack. As part of this convulsive tendency must be reckoned laryngismus stridulus and tetany with their almost constant accompaniment—the so-called "facial irritability."

In laryngismus stridulus, a spasm of the larynx suddenly closes the glottis so that the infant is for a few seconds unable to draw air into the chest: the face becomes livid, the infant looks terrified, and makes violent efforts to inspire. After a few seconds the spasm relaxes and a deep inspiration is taken with a loud crowing noise. These attacks come on usually when the infant begins to cry or just as it wakes, or a sudden draught of cold air may start the attack. There may be many in the day, or only two or three in a week. If the spasm is prolonged many seconds, the infant becomes cyanosed and may pass into a general convulsion, or may die silently of asphyxia. These attacks occur most often between the ages of six and eighteen months; they are rare after the age of two years. Of 35 cases, 32 showed definite rickets, 2 probable rickets; only 1 showed no bone manifestations of rickets.

Tetany, a tonic spasm affecting chiefly the muscles of the forearm and hand, and leg and foot, is in young children almost always associated with rickets. The hand is generally slightly flexed at the wrist, the thumb is adducted so that its tip points to the interval between the ring- and the mid-finger, the rest of the fingers are semi-flexed at the metacarpophalangeal and extended at the phalangeal joints, often with some tendency to overextension at these latter. The toes are crowded together in a position as far as possible resembling that of the fingers; the foot is sometimes extended at the ankle. Apparently from some pressure on veins by the contracting muscles, œdema of the hands and feet is often seen with the tetany. The spasm of tetany is in some cases persistent for several hours or even for days; in others it is intermittent, lasting only a few minutes at a time and causing some cramp-like pain each time it recurs. It is most frequent at the age at which laryngismus stridulus is common, and is usually associated therewith.

A latent form of tetany is not uncommon in rickety children; it is demonstrated by the method described by Trousseau: the upper arm is firmly grasped in such a way as to compress the vessels and nerves on the inner side of the arm, and after a period varying from thirty seconds to about two minutes, the hand assumes the characteristic position of tetany.

¹ *Lectures on Rickets*, Vol. iii, p. 416.

Of 24 cases of tetany in young children, 22 showed definite rickets, 1 doubtful rickets, and 1 no bone manifestations of rickets. Twenty-three of these cases were associated with laryngismus stridulus.

Facial irritability, Chvostek's sign, is also closely related and particularly to the convulsive manifestations. On gentle tapping over superficial branches of motor nerves, a contraction of the corresponding muscles occurs. This was first described with regard to the face, but is to be seen in the limbs also. Of 35 cases of laryngismus stridulus, 33 showed this nerve irritability; and it is almost always present with tetany whether this is associated with laryngismus stridulus or not. Facial irritability is found in rickets also apart from laryngismus stridulus and tetany, and is then probably always an indication of a convulsive tendency. In some of these cases there is a history of preceding convulsions; in others, after the facial irritability has been observed, convulsions occur. It is therefore of practical value as indicating the need for such drugs as bromides, by which convulsions may be averted. This nerve irritability is probably most common in the face, but as the writer has notes of cases in which it was in the limbs only, the term facial irritability is not sufficiently conclusive.

Head nodding with nystagmus (*spasmus nutans*) needs only to be mentioned here, for, although it is generally associated (Hadden, J. Thomson), the rickets is regarded only as a predisposing cause.

The pronounced nervous instability may show itself in other ways,—a rhythmic head-rolling upon the pillow so that the back of the head is rubbed almost bald, or a head-banging in which the child beats its head with its hands or against any object near, are both seen most often in rickety children, although the determining cause may be some peripheral irritation, dentition, or middle-ear catarrh.

Hydrocephalus was regarded by Jenner as sometimes produced by rickets but this view is now generally discarded. The large head of rickets, especially when the square shape is less pronounced than usual, may simulate hydrocephalus, but is probably rarely, if ever, due to distension of the ventricles.

The association of zonular or lamellar cataract with rickets, and especially with convulsions, has been noticed by several observers since Davidson and Horner of Zurich first drew attention to it in 1865.

Tenderness.—It is generally stated that there is some tenderness present not only in the bones but also in the muscles (Gee). Hilton Fagge described this as one of the characteristic features. If such a condition occurs at all, it must be quite exceptional. The rickety child is often fretful and nervous, resents, or is frightened by, any examination; but if there is definite tenderness, the presence of scurvy with the rickets should be suspected.

Gastro-intestinal Symptoms.—The abdomen is usually distended so that the rachitic "pot-belly" has become a recognized term. The distension is due to three causes,—flatulence arising from improper feeding; displacement downward of the liver and spleen by eversion of the lower ribs; diminished space in the small pelvis; probably to these may be added relaxation of the abdominal muscles so that they afford less support than normal.

As a result of this distension, the recti muscles are often separated so that there may be a gap of 1 inch (2.5 cm.) between them, where the abdominal wall is puffed out in a bulging ridge when the child lies on its back putting the abdominal wall on the stretch; but this is not peculiar to rickets; it occurs in young children with chronic distension of the abdomen from any cause.

In the gastro-intestinal, as in the pulmonary mucosa, there is a special tendency to catarrh.

The liver is often to be felt 1 inch (2.5 cm.) or more below the costal margin, but this is due in many cases, partly at least, to displacement downward by eversion of the ribs. The spleen, for the same reason, is often felt $\frac{1}{2}$ to 1 inch (1.5 to 2.5 cm.) below the costal margin; it is probably but seldom enlarged to any considerable extent, unless the condition known as splenic anæmia is to be regarded as a manifestation of rickets. Küttner found the spleen enlarged in 44 out of 60 cases; in 33 it was just palpable; in 9 it was two finger-breadths below the costal margin and in 2 there was great hypertrophy.

Respiratory System.—The laryngeal spasm has already been described. Bronchitis is very frequent in rachitic children, and this tendency is favored, in severe cases, by the softness of the ribs and the weakness of the respiratory muscles. There is, in fact, a vicious circle. For the mechanical reasons mentioned, the lung is very imperfectly filled with air and the collapse thus induced favors the occurrence of bronchitis and hence further collapse. The movements of the diaphragm also must be rendered less extensive by the eversion of the lower ribs, and at the same time hampered by the abdominal distension.

Circulatory Symptoms.—Anæmia is common and sometimes very profound. In severe cases, the child may have a waxy complexion not unlike that of chlorosis and Hutchison has referred to cases in which the blood changes corresponded. In a rickety infant aged one year and seven months, the blood showed four million red corpuscles and only 20 per cent. hæmoglobin; in another child, aged three years, with rickets, the red cells numbered five million, the hæmoglobin was only 31 per cent. The leukocyte count shows nothing characteristic; some observations by Thursfield and Drysdale¹ gave the following results: Hæmoglobin, 44 per cent.; red corpuscles, 4,364,000; white corpuscles, 11,000; polymorphonuclears, 49.2 per cent.; lymphocytes, 46.8 per cent.; large mononuclears, 3.3 per cent.; eosinophiles, .5 per cent.; myelocytes, 0; occasional nucleated red corpuscles. This would agree very nearly with the average proportions of the differential count for a healthy infant of about twelve months, except perhaps for a very slight increase of polymorphonuclear cells.

A systolic bruit is frequently heard over the open anterior fontanelle, and was formerly thought to be of value in the diagnosis between a rachitic and a hydrocephalic head (Rilliet and Barthez). It is, however, as Osler² has shown, frequent in infants and young children who are free from rickets; it is heard most commonly in the second year of life but may be heard as late as the sixth year.

Complications.—Bronchitis has already been mentioned as extremely frequent. Bronchopneumonia is also common and is one of the chief

¹*Med-Chir. Society Transactions*, 1904.

²*Boston Medical and Surgical Journal*, CIII, No. 2, p. 29.

sources of danger to life, especially where there is much rachitic deformity of the chest.

Gastro-intestinal catarrh and diarrhoea are common accompaniments and considerable dilatation of the stomach is sometimes evident both clinically and postmortem.

Infantile scurvy is an occasional complication, but the association is to be regarded as a coincidence; there is no essential connection.

Diagnosis.—The clinical picture of severe rickets is so striking that it can hardly be mistaken. The projecting rickety rosary, the large epiphyses, the large square head, the bent limbs, are characteristic enough; but in slight cases the difficulty is greater and it is clear from a comparison of various observers' statistics that there is no general agreement as to what constitutes evidence of rickets. For instance in Munich, at the same institution, one observer found about 70 per cent. of the children under two years to be rickety; another observer found that less than 5 per cent. of the children were rachitic.

Beading of the ribs has often been accepted as evidence of rickets, but this is not necessarily so: it is common to find beading of the ribs in healthy infants just after birth, and Escher found on microscopic examination that these showed none of the characteristic changes of rickets. Yielding of the skull bones on pressure, a diffuse thinness along the edge of the bones with some separation of sutures, has been taken as a proof of rickets, but this also is incorrect. A simple delay of development occurs quite apart from rickets and Fede and Finizzio concluded from a microscopic examination of the skull bones that the yielding of the skull in newborn infants was not necessarily due to rachitic change.

It seems probable that there are other bone diseases which may cause softening of bones or deficiency of calcification, so that bending or fracture of bones results. Osteomalacia, or mollities ossium, in which at an age usually beyond puberty the bones show progressive softening so that they bend in all directions, is probably quite distinct in its pathology as it usually is in its course. Occasionally cases are seen in childhood with extreme softening and bending of bones and lacking the usual characteristics of rickets, such as the enlarged epiphyses and the large square head. Some of these cases are probably much nearer allied to the so-called osteomalacia of adults. It may be that in some cases a condition like the osteoporosis produced experimentally in puppies occurs in children also.

The weakness of the limbs may be mistaken for infantile paralysis; the general distribution, the gradual onset, the retention of reflexes and the changes in the bones will usually suffice for the distinction.

The kyphosis may be so marked as to suggest spinal caries; it is generally taught that the curve of rickets disappears when the child is held up supported under the armpits, whereas that of spinal caries remains. In long-standing cases, however, the kyphosis may not disappear thus, nor even when the child is made to lie on its face, and the diagnosis has to be made from the more general curving of the spine and from the association of the kyphosis with marked rickets elsewhere.

The enlargement of the head is sometimes difficult to distinguish from that due to hydrocephalus. As a rule the flattening of the vertex and the square shape distinguish the rachitic head from the more globular hydro-

cephalic head; but there are cases in which, if the child is first seen after the fontanelle and sutures have closed, the diagnosis may be impossible; and it is only when symptoms result from increasing tension in the ventricles that the question may be settled.

Course and Prognosis.—Rickets is readily amenable to treatment, and when once the disease has stopped, any recrudescence is very exceptional. Probably, some of the cases described as late rickets are of this nature. The intensity and duration of the symptoms vary chiefly according to the feeding; no doubt, in some cases as the child grows older and takes a more varied diet, which happens to include a sufficient proportion of the requisite constituents, the disease comes to a stand-still without special treatment. In others it progresses so rapidly that within a few months considerable softening and bending of bones occurs, nervous and respiratory symptoms become pronounced, and the child dies. When death results from rickets, the immediate cause is usually bronchitis or bronchopneumonia, convulsions, or laryngismus stridulus.

Rickets is seldom seen in active progress after the age of three years, but the deformities produced may last for life. In their slighter degree however, some of these may disappear: the beading of the ribs is gradually lost in many cases and even considerable deformity of the chest may diminish greatly as the child becomes stronger and expands his lungs more thoroughly. Slight curvature of the legs may right itself if the child is kept off his feet for several months while suitable treatment is used.

Treatment.—Prophylaxis.—Rickets is in large measure a preventable disease, and as it is due chiefly to faults of diet so its prevention depends almost entirely upon dietetic measures. The surest safeguard is the continuance of breast feeding alone for nine or ten months, and the use of fresh milk as the chief article of diet until the end of the second year. It is important to realize that breast feeding does not protect from rickets when other food is given at the same time. An infant suckled, and at the same time receiving farinaceous food, often develops a marked degree of rickets. Even when an infant has been suckled entirely for the first nine or ten months, this does not prevent the onset subsequently if the feeding is then unsuitable. It is probable that the liability becomes gradually less after the end of the first year; in other words, of the large number of cases seen in the second year, most have had their onset at some period within the first twelve months; but there are certainly some in which the disease began in the second year. For this reason the diet in the second year requires care as well as in the first. A common fault is to allow the child much farinaceous food to the neglect of milk. Milk should certainly be the staple diet until the child is two years old.

There is no doubt that the early use of farinaceous food plays a large part, and it is the writer's belief that even the small proportion of starch present in barley-water has this tendency and should, therefore, be avoided during the earlier half of the first year. Few infants are the better for any starch addition to the diet before the age of nine months, and even then its introduction should be very gradual. It should be added first only to one meal daily, and when the infant is twelve months old should not be given in more than two meals. The rest should consist of milk to which raw meat juice may be added. The yolk of an egg, lightly boiled,

may also be allowed at this age. Potatoes are to be avoided altogether until the age of eighteen months, and even then only very little, thoroughly mashed with milk, should be allowed. During the second year the child should not take less than one and one-half pints (about one liter) of milk daily.

Where hand-feeding is inevitable, careful modification of fresh milk is necessary. It is not sufficient to order cow's milk diluted with water; the proportions must be properly adjusted. It is not uncommon to find marked degrees of rickets in children who have had no starch whatever but have been given equal parts of milk and water up to the age of nine or ten months, with no addition of cream. The fault in such cases is probably the deficiency of fat, and for this same reason rickets is a common result of many of the proprietary foods whether mixed with fresh milk or not and whether containing starch or not. It would seem that a proportion of fat under 2 per cent. for infants over the age of six months involves some risk, and that a proportion of fat under 1.5 per cent. given for several months at any period of infancy involves a high probability of rickets. The addition of cream to the diluted milk is an important preventive measure, and if circumstances make this impracticable, the milk should be given as little diluted as possible. Where deficiency of fat is combined with the too early use of starch or with excess of carbohydrate, as in many of the proprietary foods, the risk is greatly increased.

Other possible factors should also be considered: the child should be out in the open air three hours daily or more if possible, and the rooms in which he lives should be well ventilated and get plenty of sunlight.

If rickets has already appeared, much may be done to prevent bending of the bones by adopting such measures as will avoid the pressure of the body or other weight upon the limbs. Standing and walking especially, should be forbidden until the remedies, dietetic or otherwise, which are employed have had time to diminish the softness of the bones and the laxity of the ligaments and muscles. This may take several weeks. The greater vigor of the child's movements, the disappearance of sweating, and the increased activity of dentition, afford some indication of the improvement; but in a general way it may be said that with a marked degree of rickets, if the child has already begun to stand before the symptoms attract attention, he should be kept off his feet altogether for at least three months from the time when treatment is begun, and if standing has not yet been acquired the parents should be instructed not to encourage the child to attempt to stand.

In severe rickets in the active stage of the disease even sitting should be discouraged, for apart from the kyphosis and lateral curvature of rickets, which are usually transitory, the occurrence of pelvic deformities is favored by the pressure from above and below incurred by the sitting position. In cases where much deformity of the chest has occurred, with sinking in of the ribs in the axillary region and prominence of the sternum and cartilages, the danger of bronchitis and bronchopneumonia is to be remembered, and every precaution taken to avoid these complications.

Therapeutics.—The most important factor is the diet. In almost all cases this requires modification, generally in the diminution or discontinuance of farinaceous food according to the age, and in increase of the fat. The latter presents difficulties chiefly amongst the poor who are unable to

afford cream or who live under such conditions that milk and cream undergo much bacterial contamination. Under such circumstances, the deficiency may be supplied by any oil or fat which is easily assimilated. Cod-liver oil is most commonly used in England but other oils, such as cotton-seed oil and olive oil, have been used; and apparently it makes little difference how the fat is supplied provided it can be digested.

There are many palatable emulsions of cod-liver oil, and any of these may be used, but it may be more convenient to use the plain oil. In either case the amount of oil given at each dose should not exceed 15 minims (.75 cc.) for an infant six months old; 20 minims (1.25 cc.) for an infant twelve months old; and 25 to 30 minims (1.5 to 2 cc.) for an infant of eighteen to twenty-four months; these doses should be given three times daily just after food. In some cases, one of the combinations of malt extract with cod-liver oil is taken better and may be more valuable, especially where some farinaceous food is being allowed, as the diastasic power of the malt assists the digestion of starch. A valuable method of administering fat is to add to the diet daily the yolk of one egg. This contains 20 to 30 per cent. of fat. It must be given very lightly boiled, otherwise it becomes indigestible. An infant of nine months can have half the yolk of 1 egg daily, at ten or eleven months the whole of the yolk can be given. After the age of twelve months, the egg can also be given in the form of custard.

In some parts of Europe, especially in Vienna, but also in America by Jacobi, phosphorus has been strongly advocated. Opinions are, however, much divided as to its value; some writers state that it is not only entirely without effect but that it produces gastro-intestinal disturbance and occasionally serious toxic symptoms. It seems probable that some, at least, of the benefit which has been attributed to phosphorus, may have been due to the oil in which it has almost invariably been given. It is usually dissolved in cod-liver oil or given in an emulsion with almond oil; $\frac{1}{200}$ to $\frac{1}{100}$ grain (.3 to .6 mg.) of phosphorus may be dissolved in 1 dram of cod-liver oil (3.5 cc.), and half this quantity may be given two or three times a day. Jacobi recommends the elixir phosphori of the U. S. pharmacopœia; of this, 6 to 15 minims (about 0.4 to 1 cc.) should be given three times daily.

Various organic and other compounds of phosphorus have been used in rickets, particularly lecithin, preparations of hypophosphites in syrup, wheat phosphates, the soluble part of bran, and many patent preparations containing phosphorus. The *syrupus ferri phosphatis* of the British pharmacopœia is used by many for rickety children over the age of twelve months; it is given in doses of $\frac{1}{2}$ to 1 dram (1.75 to 3.5 cc.). Glycerin extract of bone-marrow has given good results in some cases. Various organic remedies have been tried, but, in most observers' hands, have proved useless. Stoeltzner advocated the use of suprarenal extract; but subsequent observations by Hönigsberger gave entirely negative results; the thymus and thyroid have also been tried, but the successes claimed for them have not been justified.

The value of baths is perhaps hardly sufficiently recognized; the child should have a warm bath at about 85° F. every morning, and while sitting in the bath should be douched with water at a slightly lower temperature, 75° to 80° F. If this is done with tact and the child gradually accustomed

to it, there should be no dislike to it, and it seems to have an invigorating and tonic effect which may be of value especially in reducing the nervous instability.

If convulsions have already occurred, or if a tendency to them is shown by the presence of laryngismus stridulus, tetany, or facial irritability, bromide should be given with cod-liver oil. Two to 4 grains (.13 to .26 gm.) of potassium bromide in 1 dram (3.5 cc.) of cod-liver oil emulsion, are given three times daily. Sometimes chloral $\frac{1}{2}$ to 2 grains (.032 to .13 gm.) is more effectual than bromide, and may be given every four or six hours.

Massage has also been advocated and is likely to be useful in maintaining the nutrition of the muscles while it is necessary to keep the child off his feet; but the massage must be extremely gentle and is less applicable to the infants under twelve months than to those who are older.

The child must be kept off its feet during the active stage of rickets, and if fat and heavy and especially if the bones of the legs already show bending, this measure may be necessary for several months. Often the only way to ensure this is to apply long splints to the outer side of the legs, the splints being sufficiently long to project well beyond the sole of the foot. They should be removed when the child goes to bed so that it may kick its legs about freely and exercise its muscles as much as possible.

CONGENITAL RICKETS.

It seems certain that rickets may be present at birth, but until recently cases of achondroplasia were described as foetal or congenital rickets, and, as Ballantyne has shown, there are several types of bone disease which occur in utero, all of which have probably been described as rickets in the past. The relation of these to rickets is uncertain but they bear so little resemblance to postnatal rickets, that it seems wise at present to consider them as something altogether distinct, although, as Ballantyne suggests, it may be that rickets occurring during intra-uterine life, would be modified according to the period of development at which it occurred.

As to the frequency of congenital rickets, there is a wide discrepancy in statistics. Feyerabend at Königsberg, among 180 new-born infants, found 68.9 per cent. rickety. Schwarz in Vienna found that among 500 new-born infants, 80.6 per cent. showed rickets. Fede and Cacace, at Naples, among 500 new-born infants, found only 1 with clinical evidence of rickets, and in another series of 475 new-born infants, Fede and Finizzio found only 3 with rickets. Personal experience at the Children's Hospital, Great Ormond Street, suggests that within the first two months after birth rickets is excessively rare.

The symptoms are those which have already been described as characteristic of postnatal rickets, but the frequency of fractures in the long bones is a notable feature of the congenital disease. Often 4 or 5 of the bones are broken and the fracture is often complete, not greenstick. Monti quotes Chaussier as having found in 1 case 42, in another 112 fractures. These are certainly not always produced during parturition for they have been found already united or in process of uniting at

the time of birth (Notta). All degrees of curvature of bones are also found. It has been stated that the rachitic distortions of the thorax are lacking in this form, but this is perhaps doubtful, for H. Ashby has recorded a case in which the typical deformity of the rachitic chest was present at the age of fourteen days in association with several fractures in the limbs.

There has been extensive failure of ossification of the skull in several of the recorded cases, a defect which some have described as *craniotabes*. It is very doubtful, however, whether such a condition bears any relation to the localized patches of *craniotabes* mentioned as characteristic of ordinary rickets where the thinning of the skull is probably due to absorption rather than to defect of formation of bone.

Infants with congenital rickets are often of premature birth and apart from this are commonly feeble, so that the prognosis must be guarded. But so far as the fractures are concerned, the outlook is good; they unite rapidly after birth. With suitable feeding the rickets rapidly improves and may even disappear entirely in a few months.

Congenital rickets is no doubt dependent upon some deficiency in the mother's blood of the constituents requisite for bone formation, and it is an observed fact that in a considerable proportion of the cases the mother has been ill during pregnancy. That the mother's health may exercise some effect, especially upon bone formation, in the *foetus*, is suggested by some experiments on rabbits in which the inoculation of the parents with the toxins of diphtheria or tuberculosis resulted in deformities of the hind limbs in the offspring (Charrin and Gley).

Treatment.—The treatment, apart from suitable fixation for the fractured bones, consists chiefly in careful feeding, at the breast if possible, otherwise with milk which has been carefully modified so as to contain a proper proportion of fat.

LATE RICKETS.

Rickets is occasionally seen as an active disease in the later period of childhood and in adolescence, and has then been described as late rickets, *recrudescent rickets*, or *rachitis tarda*.

Probably the term *recrudescent rickets* most accurately describes the majority, for usually the patient has shown evidence of rickets within the first two years of life and then after years of quiescence the disease has again started into activity. Much more rarely rickets makes its first appearance at this later period.

Whether *recrudescent* or not, this late rickets is very rare; but it is said by some surgeons that adolescents at the period of rapid growth not infrequently show slight bending of bones, and this has by some been described as rickets. Apart however from the curvature of bones, such cases usually show no other evidence of rickets and it seems very doubtful whether a mere failure of the hardening process in bone to keep pace with the rapid growth of bone at this age should be considered evidence of rickets. There is no doubt that bending of bones resembling that seen in rickets may occur quite apart from the histological characters of rickets. Stoeltzner's experiments have already been mentioned. He produced bending of limbs in puppies by a special diet but microscopic examination showed that the changes were not those of rickets.

Late rickets has occurred most often between the age of nine and fourteen years, but it has begun as late as seventeen years. At what age rickets should be described as late, has not been settled. Probably the disease beginning or recrudescent after the age of four years, might properly be described thus.

Symptoms.—The symptoms are similar to those already described, but the onset has usually been with some pain in the limbs, more or less severe, especially in the legs. At the same time there has been weakness so that in some cases the patient has been unable to walk without assistance.

The ribs become beaded and the epiphyses enlarged, as may be seen in the accompanying Fig. 74 of a boy aged nine and three-fourths years, in whom the symptoms of rickets, after remaining almost quiescent since his earliest years, became active again at the age of nine and one-half years. He was under the care of my colleagues, R. Hutchison and A. E. Garrod, at the Children's Hospital, Great Ormond Street. There was no enlargement of the head in this case, and this appears to be the rule; only 1 case has been recorded in which the head became enlarged during late rickets (James).

The thorax has become distorted in some cases with deformity described as typically rachitic. The bending of the lower limbs is sufficient generally to cause a waddling awkward gait. With the *x*-rays, the bones give a less marked shadow than normal, presumably from deficiency of calcification.

Examination of the urine in one case (James) showed excessive excretion of lime (more than twice the normal). The amount of phosphoric acid was fully up to the normal but hardly excessive. Irregular pyrexia was noted in one case (Cautley) during the progressive stage of the disease.

Like rickets at an earlier age, the late form of the disease hinders growth and development, the establishment of puberty may be delayed, and the child remain undergrown. Hitherto no explanation of these cases of late rickets has been found. It has been stated in some cases that there was no obvious fault in the diet; in some cases a severe illness has preceded the onset of the symptoms.

Prognosis.—Prognosis must be guarded, for the deformity is often considerable; the disease is, however, rarely fatal. There seems to be less

FIG. 74.



tendency to respiratory complications than in rickets during the first two years of life.

Treatment.—The treatment which has been found most effectual is similar to that used in ordinary rickets, namely, the administration of cod-liver oil, to which some have added phosphorus. After the disease has become quiescent, operative measures may be required for the correction of deformities.

CHAPTER XXXIV.

SCURVY (SCORBUTUS).

By ROBERT HUTCHISON, M. D., F. R. C. P. (LOND.)

SCURVY may be defined as a general disorder of nutrition characterized by debility, mental apathy and anæmia, with sponginess of the gums, ulceration of the mouth, and a tendency to hemorrhages into the subcutaneous tissues and from mucous surfaces.

History.—Good historical accounts of the disease have been given by Budd¹ and by Hirsch.² Scurvy does not seem to have been clearly recognized in Greek and Roman times though some passages in the writings of Hippocrates may perhaps refer to it, especially where he speaks of “a condition marked by foul breath, gums receding from the teeth, bleeding from the nose, and ulcers of the legs.” The earliest description of the disease as we now know it does not occur until the year 1260, when a severe outbreak occurred amongst the troops of the Christian Army fighting in Egypt under Louis IX.³ The historian of that campaign, himself a sufferer from the disease, describes clearly all the chief symptoms—bleedings from the gums, black spots on the legs, epistaxis, debility, and a tendency to syncope. In later periods good descriptions of land scurvy are found in various writings of the sixteenth and seventeenth centuries, notably in the history of the northern nations, by Olaus Magnus, and in the writings of the three physicians, Roussens, Echthius and Wierus. It is noteworthy that these writers recommend the same remedies as are at present in use against the disease. From that time down to the present day accounts of scurvy are constantly met with, especially as occurring in besieged garrisons and among troops exposed to the privations of war, conditions in which outbreaks still most frequently occur.

The earliest report of the occurrence of scurvy on board ship is contained in the *Narrative of the Voyage of Vasco de Gama Round the Cape in the Year 1497*, in which about 100 of his men, out of a total of 160, died of the disorder. About this period, when long voyages became frequent and fresh food was unobtainable on board ship, scurvy developed into a terrible scourge of the sailor and the accounts of the voyages of most explorers abound with references to it.

It prevailed, indeed, down to the year 1795 when, on the initiative of Sir Gilbert Blane, lime juice was introduced into the Navy, after which scurvy rapidly declined in that service though it is still met with occa-

¹ *Tweedie's System of Practical Medicine*, 1840, v, p. 58.

² *Handbuch der historisch-geographischen Pathologie*, Stuttgart, 1883. 26 Aufl. Abth. ii, p. 354.

³ *Histoire de Louis IX par le Sieur Joinville*, Trans., vol. i, p. 162.

sionally even now in ships of the Mercantile Marine. The rarity of the disease, however, is shown by the fact that in the last ten years only 22 cases have been treated in the Seamen's Hospital at Greenwich.

Etiology.—The true causation of scurvy is still rather obscure. It will be convenient to consider in order the different views which have been entertained.

1. That Scurvy is Due to a Deficiency of Potassium in the Blood.—This hypothesis was first put forward by Alfred Garrod.¹ Guided presumably by the Hippocratic axiom "*curationes naturam morborum ostendunt*" he analyzed diets known to have antiscorbutic properties and found that they differ from those which tend to produce scurvy chiefly in containing larger quantities of potassium. Proceeding further he found that potassium salts were diminished in amount in the blood and urine of patients suffering from scurvy, and putting the two facts together he formulated the above-stated hypothesis as to the causation of the disease. It was soon shown, however, that his view, in this simple form at least, was untenable, for, as Ralfe pointed out, beef-tea, though it contains a large quantity of salts of potash, has no antiscorbutic power and, further, the crucial test of administering nitrate of potassium to patients suffering from scurvy failed to show that it was possessed of any curative influence.

Buzzard² modified Garrod's hypothesis by suggesting that it is not potash as such but the form in which it is combined which is of importance, and it was to the organic salts of potash that he attributed the antiscorbutic power of fresh vegetables. "All antiscorbutic juices," he says, "contain salts of citric, tartaric or malic acids, and we have no evidence of any substances which contain these materials in considerable quantity, and are yet deficient in the power of preventing scurvy. The mode by which they act is still involved in obscurity." Subsequent investigations have been directed to the clearing up of this obscurity and have led to the adoption of the following view:

2. That scurvy is caused by a diminution in the alkalinity of the blood, or, in other words, that it is to be regarded as an acid intoxication.

This hypothesis was first put forward by Ralfe,³ who concluded from his analyses of the urine of patients with scurvy and that of healthy persons after the withdrawal of fresh vegetables from the diet:

1. That the primary change that occurs in scurvy is a chemical alteration in the quality of the blood.

2. That this chemical alteration as far as can be judged from inferences drawn from the analysis of urine in patients suffering from scurvy, and analysis of scorbutic and antiscorbutic diets, points to a diminution of the alkalinity of the blood.

3. That this diminution of alkalinity is produced in the first instance (physiologically) by an increase of acid salts (chiefly urates) in the blood, and finally (pathologically) by the withdrawal of salts having an alkaline reaction (chiefly alkaline carbonates).

4. That this diminution of the alkalinity of the blood finally produces the same results in scurvy patients as happens in animals when attempts are made to reduce the alkalinity of the body (either by injecting acid

¹ *Edinburgh Monthly Journal of Medicine*, 1848, New Series, ii, p. 457.

² Reynolds's *System of Medicine*, 1866, vol. i, p. 731.

³ "An Inquiry into the General Pathology of Scurvy," *Lancet*, 1877, ii, p. 81.

into the blood or feeding with acid salts); namely, dissolution of the blood corpuscles, ecchymoses and blood stains on mucous surfaces, and fatty degeneration of the muscle of the heart, the muscles generally, and the secreting cells of the liver and kidney.

This conception of the disease has been independently advocated by A. E. Wright, whose line of argument is as follows:¹ "The scorbutic condition is a pathological condition which is induced by a dietary consisting of meat and cereals to the exclusion of green vegetables, tubers and fruits. Inasmuch as the foodstuffs which are excluded from the dietary in question are foodstuffs which contain an excess of bases over mineral acids, while the foodstuffs (meat and cereals) which remain are foodstuffs which contain a large excess of mineral acids over bases, it is obvious that the scorbutic condition is one which supervenes upon the ingestion of a considerable excess of mineral acids over bases. It would, in view of this consideration, seem probable that scurvy is a condition of acid intoxication very similar to the acid intoxication which can be experimentally produced in herbivora by the ingestion of a surplus of mineral acids. The theory that scurvy is essentially a condition of acid intoxication would appear to be in harmony with the circumstance that the rapidity with which the scorbutic condition supervenes depends apparently upon the degree to which the mineral acids are in excess in the dietary. The condition is apparently more rapidly superinduced by a dietary of corned meat (*i. e.*, meat which has been rendered hyperacid by the removal, in the process of corning, of the alkaline salts of the blood and lymph) than by a dietary of fresh meat (*i. e.*, meat which still contains these alkaline salts). Justification for the identification of scurvy with a condition of acid intoxication would appear to be afforded also by the consideration that the scorbutic condition is remedied or alleviated by the addition to the scorbutic dietary of any one of a whole series of different substances—tubers, green vegetables, decoctions of leaves and growing shoots, blood (used for this purpose by the Laps), fruits and fruit juices—substances which have apparently in common only the circumstance that they all contain an excess of bases over mineral acids." In confirmation of this view Wright found that there was a striking reduction in the alkalinity of the blood in a series of scurvy cases which he examined and that as the condition passed off the alkalinity rose again to normal.

3. The view that scurvy is caused by poisoning with ptomaines was first put forward by Torup, of Christiania, and has been investigated experimentally by Jackson and Vaughan Harley.² They argue from the experience of Nansen in the Arctic regions that scurvy cannot be due to a diet devoid of fresh vegetable constituents and exposure to insanitary surroundings, for Nansen was subjected to both these conditions and yet escaped the disease. They also advance evidence to show that the disease is not prevented by the consumption of lime juice but that it is associated with the eating of tinned or salted meat. They then describe experiments upon monkeys fed upon a diet of boiled rice or maize to which was added a proportion of tinned meat given either fresh or after being kept until it was slightly tainted. The monkeys which were fed on

¹"On the Pathology and Therapeutics of Scurvy," *Lancet*, 1900, ii, p. 565.

²*Lancet*, 1900, i, p. 1184.

the tainted meat developed sponginess of the gums, and diarrhoea with blood and mucus in the stools. Interesting as these experiments are it would be rash to conclude that we have here an exact reproduction of the disease as it occurs in the human subject. It is to be noted, for instance, that in none of the animals was there any swelling or tenderness of the limbs or appearance of purpuric spots, and in any case the diet above described must be regarded as so abnormal for monkeys that it would be unwise to draw conclusions from its effects upon them as to the results which it might be expected to produce in the human subject.

4. The view has recently been gaining ground **that scurvy is the result of a specific infection** which takes place through the mouth.

The earliest attempts to cultivate a microorganism from the cases of the disease were made by Murri,¹ Contu,² and Wieruszkij,³ but yielded no definite results. Babes,⁴ however, was more successful and succeeded in reproducing some, at least, of the features of the disease in rabbits by injecting them with cultures taken from the gums of patients suffering from scurvy. He demonstrated, also, in the blood of his cases, a bacillus which he believed to be the cause of the disease. He describes it as being narrower, and considerably longer than the cholera bacillus, pointed at the ends, and not staining by Gram's method. It is probably always present in the mouth.

Myer Coplans⁵ strongly supports the infective view of the origin of scurvy as the result of his experience of the disease in the Concentration Camps during the Boer War. He found that the disease prevailed directly as the habits of the occupants of the camps were filthy, and could trace no relation between its prevalence and the character of the diet; the disease might be present in one camp and not in another although the rations of the two were identical.

Summing up all the evidence, it seems probable that whilst a deficiency of fresh vegetables, *i. e.*, of organic salts of potash, plays a part in the production of the disease by reducing the alkalinity of the blood, yet this does not afford a complete explanation of the occurrence of all the symptoms, and it is not unlikely that upon the soil so prepared there is grafted some specific infection which finds access to the body by the mouth. Insanitary surroundings, overwork, mental depression, and exposure to cold and damp, facilitate the development of the disease by lowering the resistance of the patient.

Morbid Anatomy.—The bodies of patients who have died of scurvy usually exhibit only a slight degree of rigor mortis, and putrefaction occurs early. The only constant morbid change found, however, is effusion of blood in various situations. These effusions, which may be diffuse or circumscribed, are met with both in the skin and subcutaneous tissues and under the periosteum of the bones and consist of altered blood which may have undergone partial clotting or even organization into fibrous tissue. Hemorrhages are also met with in the pleura and pericardium and though more rarely, in the peritoneum as well. There may also be

¹*Riv. Clin. di Bologna*, 1881, 3s. i, p. 215.

²*Raccoglitore Medico*, 1881, xvi, p. 188.

³*Wratsch*, 1890, pp. 208 and 303.

⁴*Deut. Med. Wochensh.*, 1893, xix, p. 1035.

⁵*Lancet*, 1904, i, p. 1714.

hemorrhagic effusion into the joints. The internal organs show no constant change but the heart muscle is soft and often degenerated. The lungs are œdematous, and may contain infarctions. The kidneys and liver rarely exhibit any signs of disease. The spleen is large, soft, and congested, and may also show infarcts on its surface. It is important to note that all accurate observations agree in showing that the bloodvessels exhibit no gross or microscopic changes.

In the altered gums, Babes distinguishes five layers: (1) A surface layer, for the most part free from epithelium, moderately thick, pale, resembling a diphtheritic membrane with a few fragments of nuclei, and containing various bacteria, especially streptococci. (2) A structureless layer, about one millimeter thick, consisting of a felt-work of long fine bacteria. (3) Uni- and multi-nucleated round cells. (4) A layer of œdematous mucous membrane containing many bacilli resembling those in the second layer. In the walls of the vessels are numerous swollen spindle-cells. (5) Large and much dilated vessels with large spindle-cells in their walls. In the blood which fills the vessels are various cell masses, numerous multi-nucleated leukocytes, endothelial and mast cells but no bacteria.

Symptoms.—Prodromal Symptoms.—Scurvy is usually a disease of insidious onset. The patient begins to suffer from loss of bodily vigor, and from an even more marked mental apathy and lassitude so that the slightest task becomes a burden. At the same time he looks ill. The face becomes pale, or sallow and drawn, the eyes sunken, lusterless and encircled by dark rings. At this period too, there may be some pitting of the ankles on pressure, and a tendency to diarrhœa whilst it may be observed that the least knock or injury tends to be followed by a bruise. He suffers also from pains of a rheumatic sort in the limbs and joints. To these symptoms there are soon added those characteristic of anæmia—shortness of breath on exertion, palpitation, and a tendency to syncope.

Such symptoms may precede by a few days or even weeks, the more characteristic signs of the disease. Amongst these the most striking though not necessarily always present, are the changes in the mouth. The gums begin to swell, especially around stumps or carious teeth, and as the process goes on the swelling may become so great as to amount to a veritable hypertrophy so that the teeth become buried in a mass of soft, fungous tissue of a bluish or purplish tint. Ulceration quickly follows along the margins, the process being accompanied by the discharge of a sanious fluid which imparts an odor of great fœtor to the breath. Finally the teeth become loosened in their sockets and may fall out whilst necrosis of the alveolar edges ensues.

Equally characteristic and constant are *hemorrhages into the skin and subcutaneous tissue* which assume the form either of petechiæ or of ecchymoses. The former occur as small red or purple spots resembling flea bites which appear first around the hair follicles of the lower extremities and impart, by the elevations which they produce, a slight feeling of roughness to the skin. They remain for about a week, and then gradually fade into greenish spots which soon disappear; their disappearance being followed by a slight degree of desquamation. The production of the petechiæ is determined by the slight irritation caused by the friction of the clothes, and hence they are always to be found first on the outer

surface of the leg, and the outer and anterior aspects of the thigh. Here and there the petechiæ may coalesce into larger areas or macule. In severe cases the slightest pressure on the skin is sufficient to cause ulceration, the ulcers having thick edges and bleeding surfaces from which a very offensive discharge is given off. Such ulcers may spread rapidly, and invade surrounding tissues, giving rise in some cases to dangerous, and even fatal hemorrhage. Ecchymoses, the other characteristic surface lesion of scurvy, are produced by hemorrhage into the subcutaneous or intermuscular tissue. They may occur spontaneously or as the result of injury, and vary greatly both in size and extent, being commonest in the lower extremities where they may form quite large swellings. The part affected by them is brawny, tender and pits on pressure, the indentation persisting longer than it does in ordinary cedema. The skin over them is red, shiny, and hot. Such effusions are common, also, in the popliteal space and in the bend of the elbow as well as in the loose tissue around the malleoli, and beneath the muscles of the jaw. In these situations they form indurated swellings which fill up the natural hollows of the part, and greatly interfere with the movements of the adjacent joint. Where such effusions occur, as they sometimes do, over the shins, they are apt to be mistaken for syphilitic nodes.

There is no marked tendency to bleeding from the internal organs in scurvy, but hemorrhages may take place from the mucous surfaces. Of such hemorrhages, epistaxis and bleeding from the mucous membrane of the mouth are commonest. Bleeding may also occur from the mucous membrane of the intestine when there is a co-existing diarrhœa. Hæmoptysis, hæmatemesis and hæmaturia are rare. Hemorrhagic effusion into the pleura and pericardium have also been described. Not uncommonly hemorrhage occurs under the conjunctiva and may be so extensive as appreciably to raise the ocular layer, leaving the cornea at the bottom of a pit surrounded by swollen and red conjunctival membrane.

As the disease progresses anæmia becomes a marked feature. The *blood* itself presents simply the characters of a secondary anæmia, and there is no leukocytosis unless secondary inflammatory complications exist. Special interest attaches to the chemical condition of the blood on which, however, but few observations have been made. If the views of Ralfe and of Wright as to the etiology of the disease are correct one would expect to find a diminution of alkalinity and of coagulability and Wright in a few cases has shown that diminution of coagulability is actually present. Barnardo, who had the opportunity of investigating this point during the Somaliland Campaign, found no constant relation between the degree of reduced alkalinity and the severity of the symptoms. Although he states that in all cases where the alkalinity is much reduced profound constitutional disturbance will soon manifest itself if it be not already present.

Alimentary symptoms are often absent. Appetite is not necessarily impaired but dyspeptic symptoms may be present as the result of the imperfect diet which produces the disease. Constipation is the rule but the conditions under which scurvy is developed frequently favor the production of diarrhœa of a dysenteric type and when such a complication exists it may be attended by bloody discharges from the bowel.

The *urine* at the outset is scanty, high-colored, turbid and occasionally albuminous but as improvement sets in it becomes more abundant and pale. The amount of free acid in it is diminished and so, it is alleged, are the potash salts.

Of the *complications* of scurvy, gangrene of the lung is one of the most frequent and dangerous. It is marked by the usual expectoration of dark foetid matter, by rapid and difficult breathing with great depression, and usually ends fatally.

Buzzard describes an affection of the chest in scurvy which may be mistaken for pneumonia. Faint rigors, followed by a certain amount of feverishness and accompanied by lancinating pain in one or both sides, usher in this condition. The pain is felt only in coughing and a very viscid mucus is expectorated. The dyspnoea increases, and a constriction as though from a cord bound tightly round the chest is described. Although it occasionally happens that these pulmonary symptoms are dependent upon true inflammation, they are much more commonly associated with the effusion of sanguineous fluid into the cavity of the pleura or into the substance of the lung itself, these structures sharing with every other organ that tendency to effusion which is the dominant feature of scurvy. When the lung is thus invaded the expectoration after a short time becomes dark and sanious, with all the horrible foetor which is ordinarily associated with gangrene of the lung, but which is here dependent upon decomposition of the bloody fluid poured into the lung substance. There are now cold sweats, increasing dyspnoea and anxiety, a small and frequent pulse, and death. In other cases there is no pain or cough but the breathing rapidly becomes short and labored and death occurs suddenly. Auscultatory signs in the lungs are usually wanting, but now and then there is localized dulness on percussion with bronchial breathing, or mucous rales are heard, sometimes also with gurgling sounds at certain parts of the chest.

Night blindness is a condition sometimes met with in patients suffering from scurvy who have also been much exposed to bright light, and may occur quite early in the disease. It would appear to be merely the result of the anæmia and exhaustion which scurvy produces and is in no sense an essential part of the scorbutic process.

Diagnosis.—If all the characteristic symptoms are present and if the disease arises simultaneously in a number of subjects in circumstances known to favor its development, the diagnosis of scurvy is easy. Difficulty only occurs when one has to deal with sporadic cases, such, for example, as the cases of land scurvy occasionally met with in badly fed individuals.

The disease which perhaps most closely resembles it is *purpura hæmorrhagica* (*morbus maculosus* of Werlhof) but in this the affection of the gums is absent and the hemorrhages have not, as they have in scurvy, an inflammatory character.

Mercurial cachexia, which in many points closely simulates scurvy, is now but rarely seen and an inquiry into the history will usually lead to a correct conclusion.

Acute lymphatic leukæmia, which is often marked like scurvy by ulceration in the mouth, can be at once distinguished by an examination of the blood.

Prognosis.—The prognosis of scurvy, except in the severest cases, is favorable, provided suitable treatment can be adopted. It has often been noted that the outlook in this disease is by no means dependent upon the severity of the lesions in the skin, mouth, and muscles, but is in far closer relation to the state of the internal organs such as the lungs and heart. The supervention of complications and of intercurrent disease also exerts powerful influence upon the prognosis whilst a speedy and often unexpected fatal result may be brought about by severe hemorrhage or heart failure.

Even in cases which run a favorable course it may be weeks or even months before the patient is restored to his original vigor, and when recovery is complete there may still be some results of the disease shown in cicatrices in the skin or partial ankylosis of joints.

Treatment.—The first point is to remove the patient if possible from the place in which the disease has developed and to bring him under more hygienic conditions. Cold and damp should especially be avoided and he should be placed in warm and dry surroundings. Of even greater importance is it to make a radical alteration in his diet. Whatever view may be held as to the causation of the disease all experience goes to show that the introduction into the diet of a sufficient quantity of fresh vegetable food has a powerfully curative effect.

It would appear that there is no particular form of vegetable food which has a specific influence over the disease but that all are equally efficacious. The antiscorbutic power of fresh limes and lemons has been known since the seventeenth century and these fruits still constitute a favorite remedy. It is important that they should be fresh; lime juice which has been bottled for some time is apt to decompose into free citric acid and carbonates and loses much of its value. An objection to lime juice is its rather acrid taste, on account of which it is sometimes found to be difficult to induce those who are exposed to the disease to take it regularly as a preventive. Lemonade made from fresh lemons is not open to this objection.

Preserved vegetables, though useful, seem to have a feeblar antiscorbutic power than fresh; sauerkraut appears to be more serviceable in preventing the disease than any other form of preserved vegetable and Captain Cook employed it successfully in some of his voyages. Infusions of malt are also powerfully antiscorbutic. Forster,¹ who accompanied Cook in his second voyage, describes a severe outbreak of scurvy and its cure of infusion of malt without any other change in the diet; he adds, "The encomiums on the efficacy of malt cannot be exaggerated." In some of the worst cases that he saw the patient took as much as 5 pints of the infusion in a day. The infusion should be fresh, for its good qualities are impaired if it is allowed to become damp and mouldy.

Fresh meat juice has been found to be of value as an antiscorbutic owing, it is alleged, to the lactates which it contains. Milk is also serviceable, 3 pints of it containing as much citric acid as 1 ounce of lime juice and instances are on record of outbreaks of scurvy which have been checked by its administration. Of beverages, French and Italian wines are stated to be antiscorbutic but opinions as to the power of cider in this respect vary considerably.

¹*Notes from a Voyage Round the World*, by George Forster, vol. i, 1777.

Drugs are of far less use in scurvy than the measures above indicated. Wright, on hypothetical grounds, has recommended the administration of Rochelle salt in doses of 30 to 60 grains (gm. 2 to 4) thrice daily until the urine is alkaline, along with 20 grain (gm. 1.3) doses of crystallized calcium chloride to increase the coagulability of the blood. Barnardo speaks favorably of this treatment as the result of his experience in Somaliland.

The administration of bitters—especially of quinine—and of iron to combat the anæmia is of help in restoring health, and special complications may require the administration of appropriate remedies. In the treatment of diarrhoea, bael fruit is stated to be specially useful.

Locally the conditions of the mouth will demand most attention. Antiseptic washes of permanganate or chlorate of potash or peroxide of hydrogen help to remove the fœtor, whilst the spongy and ulcerated gums may be painted with a strong solution of nitrate of silver. Absorption of local effusions of blood may be promoted by gentle massage.

The *prophylactic treatment* consists in attention to general hygienic conditions and in the provision of an abundant and varied dietary containing an adequate proportion of vegetables. In Nansen's Arctic expedition, which lasted three years and during which scurvy was entirely avoided, the diet consisted of meat of various sorts in hermetically sealed tins, dried fish, potatoes both dried and tinned, all sorts of dried and preserved vegetables and fruits, jam, marmalade, condensed milk, preserved butter and desiccated soups. Flour was carried to make fresh bread. Drinks consisted of tea, coffee and cocoa, beer and lemonade.

Lime juice has long been used as a prophylactic but is apt to undergo decomposition when kept long in a barrel. Two ounces twice a week is recommended as a preventive dose.

INFANTILE SCURVY.

That infantile scurvy is closely related to the adult form of the disease there can be little doubt, and as in the latter there is reason to believe that a deficiency of vegetable salts in the food plays an important part in its development. None the less the clinical manifestations of the two forms are very different, but the differences are probably to be explained by differences of diet and by the anatomical and physiological peculiarities of the infantile period of life.

Historical.—As far back as the middle of the seventeenth century Glisson, in his *Treatise on the Rickets*,¹ had already given a clear description of scurvy occurring as a complication of rickets but the disease seems to have been lost sight of until two centuries later when Möller² described some cases under the title of "acute rickets" a term which was adopted by other continental writers on the subject, such as Bohn, and Hirschsprung. In 1873 Jalland³ described a case in a child of ten months and considered it as identical with the scurvy of adults.

¹English Trans., 1651, p. 249.

²Königsb. *Med. Jahrbücher*, 1859, i, p. 377.

³*Med. Times and Gazette*, 1873, i, p. 248.

Another case was published in 1876 by Thomas Smith who described it as one of "Hemorrhagic periostitis of several of the long bones with separation of the epiphyses,"¹ but failed to recognize its scorbutic nature. To Cheadle belongs the credit of first clearly emphasizing the identity of such cases with the scurvy of adults, which he did in a paper on "Three Cases of Scurvy Supervening on Rickets in Young Children,"² published in 1878. In 1881, Gee³ published a series of cases under the name of osteal or periosteal cachexia, but in 1882 Cheadle⁴ again insisted upon the identity of such cases with scurvy. A year later Barlow secured general recognition of the truth of Cheadle's views by a paper entitled, "On Cases Described as 'Acute Rickets' Which are Probably a Combination of Scurvy and Rickets, the Scurvy Being an Essential and the Rickets a Variable Element."⁵ This paper contained an exhaustive clinical and pathological account of the disease and has become a classical publication of the subject which on the Continent has secured for infantile scurvy the title of Barlow's Disease. The terms "acute rickets" and "scurvy rickets" are still sometimes used but all later observations tend to show that the rickety element is a mere complication and not an essential part of the process. The latest and most exhaustive account of infantile scurvy was written by Cheadle,⁶ but almost every day adds to the literature of the disease.

Etiology.—Clinical observation shows that the vast majority of cases of scurvy arise in infants who are being fed on a diet which is deficient in *fresh* constituents. The diet which most commonly produces the disease seems to be one consisting of condensed milk with the addition of a tinned food, but a diet of sterilized milk alone is undoubtedly capable of giving rise to it, and so even may milk which has merely been boiled. Griffith,⁷ in summarizing the results of an investigation of 356 cases collected by a committee of the American Pediatric Society, with the addition of 18 cases of his own, concludes that in 60 per cent. a proprietary food had been used but often with the addition of sterilized milk. Nine per cent. had been fed on condensed milk and 19 per cent. on sterilized milk only.⁸ Pasteurized milk seems much less apt to produce the disease. That the want of freshness in the food is not the *only* cause of the disease, however, seems to be shown by the fact that 10 of the cases had been fed on the breast only and several of them on raw milk.

It may be asked, What is it, in a diet deficient in fresh constituents, which tends to produce infantile scurvy? That the fault is a negative and not a positive one, that is to say, due to the absence from the food of some constituent which it should contain rather than to the presence of some abnormal element, is shown by the fact elicited by some observations made

¹ *Transactions of the Pathological Society of London*, xxvii, 1876, p. 219.

² *The Lancet*, 1878, ii, p. 685.

³ *St. Bartholomew's Hospital Reports*, vol. xvii, p. 9.

⁴ *The Lancet*, 1882, ii, p. 48.

⁵ *Trans. Royal Medical and Chirurgical Society*, 1883, lxvi, p. 159.

⁶ *Allbutt's System of Medicine*.

⁷ *New York Medical Journal*, 1901, lxxiii, p. 317.

⁸ For additional evidence for the production of scurvy by sterilized milk, see Netter (*Scorbut infantile et lait stérilisé*) *Rev. des Maladies de l'Enfance*, xx, p. 543, 1902; Neumann, *Deut. Med. Woch.*, 1902, xxviii, pp. 628, 647; and Ashby, *Brit. Med. Journ.*, 1904, i, p. 479.

by the writer¹ that the mere addition of sterilized fruit juice to the diet without any other alteration, exercises an undoubtedly curative influence. The same was found to be true, though in a lesser degree, of the vegetable salts of potash when administered artificially. It would seem probable that a deficient supply of vegetable salts plays at least a large part in the causation of infantile scurvy just as it does in that of the adult form of the disease. Milk contains a considerable quantity of citrate of lime; and Corlette² has pointed out that this salt is present in fresh milk in the amorphous and more soluble form, its solution being aided by the presence of phosphates, but that when milk is boiled the amorphous is converted into the crystallizable form of the salt, which is less soluble and separates out. The mere boiling and, *a fortiori*, the sterilization of milk causes it to become poorer in citrates than it ought to be, and to this he attributes the tendency for scurvy to develop when such milk is exclusively used.

How it is that a deficiency of vegetable salts in the food leads to the hemorrhagic tendency characteristic of scurvy we do not know. It is not, apparently, by reducing the coagulability of the blood, for (as already pointed out) the coagulation time in cases of scurvy is not longer than the normal. It is more likely that the hemorrhages are in some way induced by a lowering of the alkalinity of the blood (according to the views of Ralfe and Wright as already stated in the section on SCURVY IN THE ADULT), although no actual proof of the existence of a diminished alkalinity in cases of infantile scurvy has yet been obtained. In favor, too, of this hypothesis is the fact that the mere withdrawal from the diet of a tinned cereal food, where such is being given and which yields an acid ash, is often sufficient of itself to lead to a cure of the disease.

There is therefore considerable reason to believe that a reduction of the alkalinity of the blood from a deficient supply of vegetable salts plays at least a large part in the production of infantile scurvy just as it does in the scurvy of adults. On the other hand there is much less reason to assume the existence of an infective element in the infantile form, for the infants who exhibit it are but rarely drawn from the poorer classes but, on the contrary, are more commonly the children of well-to-do parents and enjoy clean and comfortable surroundings.

Morbid Anatomy.—The chief changes found after death, in infants who have died of infantile scurvy, are present in the neighborhood of the bones. If a section be made across a limb which has been the seat of swelling during life it will be found that the periosteum is thickened, highly vascular and separated from the subjacent bone by a layer of blood clot which may show various degrees of organization. There is, however, no sign of inflammation and as a rule no hard bone is formed in the periosteum except in very old-standing cases. The muscles surrounding the bone may be infiltrated with blood or serum, which gives them a sodden appearance.

The bone itself exhibits a considerable degree of rarefaction, the cancellous tissue being unusually porous and the normal marrow replaced by a highly vascular connective tissue into which hemorrhages may have

¹Goulstonian Lectures for 1904 on Some Disorders of the Blood and Blood-forming Organs in Early Life.

²British Medical Journal, 1900, ii, p. 573.

occurred. The changes characteristic of rickets may also be present in the bones.

The rarefaction of the bone is apparently the result of delayed ossification and is the cause of the fractures which are not uncommonly met with in severe cases and which are usually situated a little above the epiphyseal line, although there may sometimes be separation at the line of the epiphyseal cartilage itself.

Hemorrhagic effusions may be met with elsewhere in addition to those around the bones, such as in the joints or in the serous cavities or subdural space. None of these, however, is characteristic of the disease. The internal organs exhibit no constant change.

Symptoms.—Scurvy is commonest in infants of about eight to ten months old. In an analysis of 64 cases by Bovaird¹ the youngest was six months old, the oldest two and a half years, the average age being twelve months. Fifty-four per cent. of the cases occurred between the ninth and thirteenth months. The children affected are usually well-nourished but often exhibit some degree of pallor. The invasion of the disease may be either gradual or abrupt. After a few days of fretfulness or after having exhibited for some time great tenderness when handled, the more prominent symptoms appear. The most striking of these is tenderness of the legs, which causes the child to scream out when touched or even at the approach of the doctor. It can be observed that the child lies very still, usually on his back with one or both legs everted and motionless. Examination in a well-marked case reveals some swelling of the bones, most commonly of the lower end of the femur or upper end of the tibia. The long bones of the upper extremities are much more rarely affected, the collective investigation in America yielding only 14 cases with swelling in the arms to 131 in which the legs were affected. At the site of these swellings the tenderness is extremely acute and the skin over them is often tense and glossy and may be slightly cedematous but there is no local heat. On gently handling the limb soft crepitus may be elicited, from fracture, or separation of the epiphysis. In some cases hemorrhage takes place into the orbit, giving rise to proptosis and ecchymosis of the eyelids. This symptom occurred in 49 out of 379 of the American cases. The proptosis may appear suddenly, often during a fit of crying, and in severe cases may even lead to ulceration of the cornea.

Rarer sites of hemorrhage are round the ribs, clavicles, or bones of the skull. Sir Thomas Barlow has described a peculiar depression of the sternum *en bloc* which is present in severe cases and is apparently due to a loosening of the articulations between the sternum and ribs.

Changes in the Gums.—These are not usually present unless some teeth have been cut, but even in the absence of the latter there may be a slight degree of injection and ecchymosis, especially over the sites of the incisors. Should any teeth have erupted, the gum around them is usually swollen and of a purplish color, but the change is rarely if ever so marked as in the scurvy of adults and does not often go on to ulceration. It is rare for the gums to appear normal after any teeth have appeared, but a few such cases have been observed.

Other Symptoms.—Petechiæ and subcutaneous ecchymoses are rarely met with in infantile scurvy and hemorrhages from mucous surfaces,

¹ *Philadelphia Medical Journal*, 1898, ii, p. 375.

with the exception of the gums, are not common. Hæmaturia, however, is met with not infrequently and a slight degree of it, at least, is probably much commoner than is generally believed. Sometimes indeed it is the only symptom present and in a few cases it appears to lead to nephritis¹ or pyelitis. Fever is not a conspicuous feature of infantile scurvy, but where extensive hemorrhages have taken place there may be a rise of temperature which, however, rarely exceeds 101° or 102° F.

Changes in the Blood.—There is usually a greater or less degree of anæmia present, especially in cases in which extensive subperiosteal hemorrhages have occurred. The anæmia is usually of the chlorotic type, the hæmoglobin being reduced out of proportion to the red cells, but where the hemorrhages have been specially severe the characters of a secondary anæmia may be exhibited as well, and the red cells are reduced in number and some nucleated forms present. In the absence of complications no leukocytosis occurs. The chemical changes in the blood have not been fully investigated but in a series of cases examined by the writer no alteration in the coagulability could be discovered. Whether or not there is any reduction of alkalinity has not been determined.

Association with Rickets.—The relation of scurvy to rickets has been much disputed. That the two conditions are not invariably associated is shown by an analysis of 40 fatal cases by Schoedel and Nauwerk² in 18 of which the presence of rickets had been recognized during life, whilst it was found in 3 others after death. The frequent co-existence of rickets in cases of scurvy would seem indeed to be due merely to the fact that the kind of diet which produces the one disease is also that which tends to give rise to the other.

Diagnosis.—The diagnosis of scurvy in a well-marked case is easy, provided the leading features of the disease are known to the observer. The screaming of the child on examination, the swelling and tenderness of the legs, and the condition of the gums leave no doubt as to the nature of the affection with which one has to deal. All cases, however, are not so pronounced in type. Not infrequently one encounters mild or incipient forms which it is easy to overlook. In these, tenderness when the child is handled or when he is put in his bath may be the only symptom. In other cases again, slight sponginess round the incisor teeth may alone be present or one may have to deal with an apparently causeless hæmaturia. In any case in which there is doubt two points will help. One is the nature of the feeding. If this has been of such a nature as is known to favor the development of the disease the diagnosis will be greatly strengthened. The other point is the application of the therapeutic test. If the symptoms present are really due to incipient scurvy then they will certainly disappear rapidly so soon as appropriate treatment is begun; if they fail to do this then one has to do with some other condition.

The affections for which scurvy is most often mistaken are these:

1. Rheumatism.—Time and again the writer has had well-marked cases of infantile scurvy sent to him with a diagnosis of rheumatism and in one such case he has known the affected limb to be painted with iodine with the result of greatly aggravating the sufferings of the unfortunate child. The mistake should really never be made if it be remembered

¹See Still, *Lancet*, 1904, ii, p. 441.

²*Rev. des Maladies de l'Enfance*, 1902, xx, p. 543.

that below the age of one year rheumatism is practically never met with. An inquiry into the mode of feeding and a careful search for the other signs of scurvy will confirm the diagnosis.

2. Periostitis.—The distinction between scurvy and periostitis is often a matter of great difficulty, especially when the gum changes are absent. The presence of a marked degree of pyrexia is in favor of a diagnosis of periostitis, for in scurvy, fever is usually absent or but trivial in amount. If the other signs of scurvy are present as well, the diagnosis will of course be clear but sometimes one may be obliged to fall back on the therapeutic test.

3. Infantile Paralysis.—When infantile paralysis sets in, as it sometimes does, with a marked degree of hyperæsthesia, it may simulate scurvy. It will be noted, however, that there is no swelling of the affected limb and that the other signs of scurvy are absent.

4. Epiphysitis.—Epiphysitis may simulate scurvy but the swelling in the latter extends along the shaft of the bone and is not confined to the neighborhood of the epiphysis.

5. The changes in the mouth may be mistaken for those of ordinary *ulcerative stomatitis*. In scurvy, however, the changes are confined to the gums whilst in stomatitis they extend to the lips and cheeks as well. The ulceration in the mouth which often occurs in acute *leukæmia* may also lead to a suspicion of scurvy. Here the examination of the blood will at once settle the diagnosis.

6. Cases which are characterized by hemorrhage into the orbit may be mistaken for *sarcoma of the skull* or for *chloroma*. In the former case there are usually signs of sarcoma elsewhere and in the latter the blood shows an excess of lymphocytes whilst in both the positive signs of scurvy are absent.

7. The *hæmaturia* of scurvy is apt to be mistaken for renal hemorrhage from other causes, such as renal sarcoma. In a doubtful case of bleeding from the kidney it is therefore always well to try the effect of an antiscorbutic diet before proceeding to other measures.

Prognosis.—The prognosis in infantile scurvy is quite favorable, provided the disease be recognized in time and suitable treatment adopted. Nothing in therapeutics, indeed, is more striking than the rapidity with which such patients improve under a change of diet although some degree of thickening of the bones may persist for a long time. Death, when it occurs in the more severe cases, is usually the result of intercurrent diseases, of which bronchopneumonia and chronic diarrhœa are the most frequent, although sudden hemorrhage, cardiac failure, or exhaustion, may occasionally lead to a fatal issue.

Treatment.—This consists solely in altering the diet. Tinned foods and sterilized milk must at once be stopped and the child put upon a due allowance of unboiled milk. Fruit juice should be added, a few teaspoonfuls of grape or orange juice sweetened with a little sugar being given daily. Baked potato is also useful, a little of the floury part under the skin being rubbed up with the milk into a thin cream which is either added to the bottle or given separately (two teaspoonfuls three or four times a day). Raw meat juice is certainly of value. It may be given in quantities of half an ounce daily. Drugs are of little service though the vegetable

salts of potash certainly exert a certain curative influence. During the period of convalescence cod-liver oil and iron are helpful.

Scorbutic infants should be handled carefully and the clothing should be so constructed that it can be easily taken off and on. If it is necessary to move the child about he should be placed on a pillow. The affected limb should be steadied by light splints or wrapped in wet towels, which, if allowed to dry in position, afford considerable support. In mild cases a casing of cotton wool secured by a light bandage will be sufficient protection.

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1. The first group of students (Group A) was assigned to the first section of the course, which was held in the morning. The second group (Group B) was assigned to the second section, which was held in the afternoon. The third group (Group C) was assigned to the third section, which was held in the evening. The fourth group (Group D) was assigned to the fourth section, which was held in the morning. The fifth group (Group E) was assigned to the fifth section, which was held in the afternoon. The sixth group (Group F) was assigned to the sixth section, which was held in the evening. The seventh group (Group G) was assigned to the seventh section, which was held in the morning. The eighth group (Group H) was assigned to the eighth section, which was held in the afternoon. The ninth group (Group I) was assigned to the ninth section, which was held in the evening. The tenth group (Group J) was assigned to the tenth section, which was held in the morning. The eleventh group (Group K) was assigned to the eleventh section, which was held in the afternoon. The twelfth group (Group L) was assigned to the twelfth section, which was held in the evening. The thirteenth group (Group M) was assigned to the thirteenth section, which was held in the morning. The fourteenth group (Group N) was assigned to the fourteenth section, which was held in the afternoon. The fifteenth group (Group O) was assigned to the fifteenth section, which was held in the evening. The sixteenth group (Group P) was assigned to the sixteenth section, which was held in the morning. The seventeenth group (Group Q) was assigned to the seventeenth section, which was held in the afternoon. The eighteenth group (Group R) was assigned to the eighteenth section, which was held in the evening. The nineteenth group (Group S) was assigned to the nineteenth section, which was held in the morning. The twentieth group (Group T) was assigned to the twentieth section, which was held in the afternoon. The twenty-first group (Group U) was assigned to the twenty-first section, which was held in the evening. The twenty-second group (Group V) was assigned to the twenty-second section, which was held in the morning. The twenty-third group (Group W) was assigned to the twenty-third section, which was held in the afternoon. The twenty-fourth group (Group X) was assigned to the twenty-fourth section, which was held in the evening. The twenty-fifth group (Group Y) was assigned to the twenty-fifth section, which was held in the morning. The twenty-sixth group (Group Z) was assigned to the twenty-sixth section, which was held in the afternoon. The twenty-seventh group (Group AA) was assigned to the twenty-seventh section, which was held in the evening. The twenty-eighth group (Group AB) was assigned to the twenty-eighth section, which was held in the morning. The twenty-ninth group (Group AC) was assigned to the twenty-ninth section, which was held in the afternoon. The thirtieth group (Group AD) was assigned to the thirtieth section, which was held in the evening. The thirty-first group (Group AE) was assigned to the thirty-first section, which was held in the morning. The thirty-second group (Group AF) was assigned to the thirty-second section, which was held in the afternoon. The thirty-third group (Group AG) was assigned to the thirty-third section, which was held in the evening. The thirty-fourth group (Group AH) was assigned to the thirty-fourth section, which was held in the morning. The thirty-fifth group (Group AI) was assigned to the thirty-fifth section, which was held in the afternoon. The thirty-sixth group (Group AJ) was assigned to the thirty-sixth section, which was held in the evening. The thirty-seventh group (Group AK) was assigned to the thirty-seventh section, which was held in the morning. The thirty-eighth group (Group AL) was assigned to the thirty-eighth section, which was held in the afternoon. The thirty-ninth group (Group AM) was assigned to the thirty-ninth section, which was held in the evening. The fortieth group (Group AN) was assigned to the fortieth section, which was held in the morning. The forty-first group (Group AO) was assigned to the forty-first section, which was held in the afternoon. The forty-second group (Group AP) was assigned to the forty-second section, which was held in the evening. The forty-third group (Group AQ) was assigned to the forty-third section, which was held in the morning. The forty-fourth group (Group AR) was assigned to the forty-fourth section, which was held in the afternoon. The forty-fifth group (Group AS) was assigned to the forty-fifth section, which was held in the evening. The forty-sixth group (Group AT) was assigned to the forty-sixth section, which was held in the morning. The forty-seventh group (Group AU) was assigned to the forty-seventh section, which was held in the afternoon. The forty-eighth group (Group AV) was assigned to the forty-eighth section, which was held in the evening. The forty-ninth group (Group AW) was assigned to the forty-ninth section, which was held in the morning. The fiftieth group (Group AX) was assigned to the fiftieth section, which was held in the afternoon. The fifty-first group (Group AY) was assigned to the fifty-first section, which was held in the evening. The fifty-second group (Group AZ) was assigned to the fifty-second section, which was held in the morning. The fifty-third group (Group BAA) was assigned to the fifty-third section, which was held in the afternoon. The fifty-fourth group (Group BAB) was assigned to the fifty-fourth section, which was held in the evening. The fifty-fifth group (Group BAC) was assigned to the fifty-fifth section, which was held in the morning. The fifty-sixth group (Group BAD) was assigned to the fifty-sixth section, which was held in the afternoon. The fifty-seventh group (Group BAE) was assigned to the fifty-seventh section, which was held in the evening. The fifty-eighth group (Group BAF) was assigned to the fifty-eighth section, which was held in the morning. The fifty-ninth group (Group BAG) was assigned to the fifty-ninth section, which was held in the afternoon. The sixtieth group (Group BAH) was assigned to the sixtieth section, which was held in the evening. The sixty-first group (Group BAI) was assigned to the sixty-first section, which was held in the morning. The sixty-second group (Group BAJ) was assigned to the sixty-second section, which was held in the afternoon. The sixty-third group (Group BAK) was assigned to the sixty-third section, which was held in the evening. The sixty-fourth group (Group BAL) was assigned to the sixty-fourth section, which was held in the morning. The sixty-fifth group (Group BAM) was assigned to the sixty-fifth section, which was held in the afternoon. The sixty-sixth group (Group BAN) was assigned to the sixty-sixth section, which was held in the evening. The sixty-seventh group (Group BAO) was assigned to the sixty-seventh section, which was held in the morning. The sixty-eighth group (Group BAP) was assigned to the sixty-eighth section, which was held in the afternoon. The sixty-ninth group (Group BAQ) was assigned to the sixty-ninth section, which was held in the evening. The seventieth group (Group BAA) was assigned to the seventieth section, which was held in the morning. The seventy-first group (Group BAB) was assigned to the seventy-first section, which was held in the afternoon. The seventy-second group (Group BAC) was assigned to the seventy-second section, which was held in the evening. The seventy-third group (Group BAD) was assigned to the seventy-third section, which was held in the morning. The seventy-fourth group (Group BAE) was assigned to the seventy-fourth section, which was held in the afternoon. The seventy-fifth group (Group BAF) was assigned to the seventy-fifth section, which was held in the evening. The seventy-sixth group (Group BAG) was assigned to the seventy-sixth section, which was held in the morning. The seventy-seventh group (Group BAH) was assigned to the seventy-seventh section, which was held in the afternoon. The seventy-eighth group (Group BAI) was assigned to the seventy-eighth section, which was held in the evening. The seventy-ninth group (Group BAJ) was assigned to the seventy-ninth section, which was held in the morning. The eightieth group (Group BAK) was assigned to the eightieth section, which was held in the afternoon. The eighty-first group (Group BAL) was assigned to the eighty-first section, which was held in the evening. The eighty-second group (Group BAM) was assigned to the eighty-second section, which was held in the morning. The eighty-third group (Group BAN) was assigned to the eighty-third section, which was held in the afternoon. The eighty-fourth group (Group BAO) was assigned to the eighty-fourth section, which was held in the evening. The eighty-fifth group (Group BAP) was assigned to the eighty-fifth section, which was held in the morning. The eighty-sixth group (Group BAQ) was assigned to the eighty-sixth section, which was held in the afternoon. The eighty-seventh group (Group BAR) was assigned to the eighty-seventh section, which was held in the evening. The eighty-eighth group (Group BAS) was assigned to the eighty-eighth section, which was held in the morning. The eighty-ninth group (Group BAT) was assigned to the eighty-ninth section, which was held in the afternoon. The ninetieth group (Group BAU) was assigned to the ninetyth section, which was held in the evening. The ninety-first group (Group BAV) was assigned to the ninety-first section, which was held in the morning. The ninety-second group (Group BAW) was assigned to the ninety-second section, which was held in the afternoon. The ninety-third group (Group BAX) was assigned to the ninety-third section, which was held in the evening. The ninety-fourth group (Group BAY) was assigned to the ninety-fourth section, which was held in the morning. The ninety-fifth group (Group BAZ) was assigned to the ninety-fifth section, which was held in the afternoon. The ninety-sixth group (Group BBA) was assigned to the ninety-sixth section, which was held in the evening. The ninety-seventh group (Group BBB) was assigned to the ninety-seventh section, which was held in the morning. The ninety-eighth group (Group BBC) was assigned to the ninety-eighth section, which was held in the afternoon. The ninety-ninth group (Group BBD) was assigned to the ninety-ninth section, which was held in the evening. The hundredth group (Group BB E) was assigned to the hundredth section, which was held in the morning.

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